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RELATION OF ARTERIOSCLEROSIS OF THE CEREBRAL VESSELS TO HYPERTENSION

DISTRIBUTION OF ARTERIES SUPPLYING PONS AND MEDULLA *

ORAN I. CUTLER, M.D.

Fellow of the National Research Council

SAN FRANCISCO

Bordley and Baker¹ have suggested that the high blood pressure observed in patients with arteriosclerosis and hypertension is the result of an attempt to provide sufficient blood for the vasomotor center from which the normal blood supply has been partly cut off by sclerosis of the vessels supplying that part of the brain. In order to provide a proper anatomic basis for further investigations along this line, I first made a study of the vessels of a series of normal brains obtained at autopsy, especial attention being paid to those of the upper portion of the medulla and the lower portion of the pons, at which level the vasomotor center is believed to be situated.² Furthermore, an attempt has been made to correlate the condition of the vessels in this region with the records of the blood pressure of the patients and with the amount of cardiac hypertrophy found at autopsy in those who had cardiovascular and renal disease. More than forty unselected brains have been examined. A number have been included in the series, as has been stated, which were from persons who had neither hypertension nor sclerosis of the vessels in the brain stem, in order to determine the normal appearance of the vessels.

The study was carried out both by making stereoscopic roentgenograms after preparations were injected into the arteries and by examining microscopic sections.

After various opaque masses were tried, one containing 125 Gm. of lead carbonate in 100 cc. of a 12.5 per cent solution of acacia was found most satisfactory and was used for injecting most of the specimens. The acacia was dissolved by gradually adding it to boiling water. It was

* From the Department of Pathology of the Stanford University School of Medicine.

1. Bordley and Baker: A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension, *Bull. Johns Hopkins Hosp.* **39**:229, 1926.

2. Ranson and Billingsly: Vasomotor Reactions from Stimulation of the Floor of the Fourth Ventricle, *Am. J. Physiol.* **41**:85, 1916.

found best to stir the mixture continuously during this process. Sufficient water was then added to make up for loss by evaporation. Lumps which might be present in the white lead were broken up, and a sufficient amount of the acacia solution to make a paste was added before the main portion was mixed with the lead. Before the mixture was used, it was filtered through muslin, which removed any small lumps and many of the larger granules of the powder. It was necessary to stir continuously while filtering.

The use of acacia allows more ready penetration than gelatin does, which must be kept warm while it is being injected, or mixtures made up in oil. The granules of lead carbonate powder are mostly below 10 microns in diameter, which makes it more desirable for injecting small vessels than such a compound as bismuth oxychloride, which contains many granules from 15 to 100 microns in diameter.³

In making the injections, a cannula was tied in one of the vertebral arteries and the other one closed by a clamp, as were the vessels leading to the cerebrum and to the cerebellum which do not give branches to the parts studied. Before injection, the vessels were washed with saline solution, as this appeared to aid the penetration of the mass. A pressure chamber connected with a manometer was used, and a pressure of from 150 to 200 mm. of mercury was usually applied. The pressure used depended on the ease with which the mass penetrated the arteries.⁴ The vessels usually filled rapidly. Although in a number of specimens collections of white lead were found in the perivascular sheaths of some of the vessels of the pons, it is believed that the rupture of the vessels was caused by trauma in removing the brain rather than by the pressure applied to the mass.⁵

After the injection was completed, the pons and medulla were severed from the cerebellum and midbrain and were hardened in 10 per cent formalin for a few days. In order that the course of the vessels in the substance of the pons and medulla might not be obscured in the roentgenograms, the portions of the injected vessels found on the surface were dissected away. Most of the pia mater was removed also. Great care was exercised not to injure the arteries by placing traction on them. Anteroposterior and lateral stereoscopic views were taken of each specimen.

Sections of the pons and the upper portion of the medulla were studied in every instance, and in most cases various other portions of the brain were also examined. In all, more than 450 sections were studied.

3. Hill, E. C.: Notes on an Opaque X-Ray Mass, *Bull. Johns Hopkins Hosp.* **35**:218, 1924.

4. Fay, Temple: *Cerebral Vasculature*, *J. A. M. A.* **84**:1727 (June 6) 1925.

5. Lampert and Müller: Bei welchem Druck kommt es zu einer Ruptur der Gehirngefäße? *Frankfurt. Ztschr. f. Path.* **33**:471, 1926.

The mass of material injected remained in the arteries during the process of preparing the slides. The smallest lumen entered by it was about 15 microns in diameter. Numerous vessels having lumina 25 microns in diameter were injected.

NORMAL ARTERIES OF PONS AND MEDULLA

Before the observations in cases in which there was either a high blood pressure or sclerosis of the vessels in the pons or medulla are discussed, a short description will be given of the distribution of blood vessels within the pons and medulla. The external origin and course of these arteries has been thoroughly studied by a number of observers.⁶ By injecting masses of colored material which outlined the various areas, Stopford⁷ was able to determine the portions of the brain stem supplied by the different arteries which provide branches that enter its substance.

Roentgenograms of the specimens injected with an opaque mass enable one to see the size and course of the arteries in the brain substance. From these, a number of drawings have been made. In each, only those vessels are shown whose point of entry is visible on the surface toward the observer. The various motor nuclei are represented in stippling. Only arteries which supply these nuclei are represented as ramifying in any of them. Anastomoses between vessels are not represented, as none were found which were large enough to be seen when the films were examined with a hand stereoscope.

Two lateral views have been prepared. One shows the vessels along the midline which might be called *arteriae mediales*. In the other, the more lateral arteries are represented. These might be spoken of as *arteriae laterales*. The vessels which enter along the midline on the ventral surface of the pons and medulla are larger than most of those which enter more laterally.

MEDIAL ARTERIES OF PONS

The points of entry of the medial branches of the anterior spinal artery form nearly a straight line along the anterior median fissure of the medulla, but in the pons most of the medial arteries are a little to one side or the other of the midline, owing to the greater diameter of the

6. Foix and Hillermand: Note sur la disposition des arteres de l'axe encephalique, *Compt. rend. Soc. de biol.* **92**:31, 1925; Les arteres de l'axe encephalique jusqu'au diencephale inclusivement, *Rev. neurol.* **2**:705, 1925. Piersol, G. A.: *Human Anatomy*, ed. 5, Philadelphia, J. B. Lippincott Co., 1916, p. 1206.

7. Stopford, J. S. B.: The Arteries of the Pons and Medulla, *J. Anat. & Physiol.* **50**:130, 1916. Shellshear, J. L.: Blood Supply of the Hypoglossal Nucleus, *J. Anat.* **61**:279, 1927.

basilar artery (fig. 3). The terminal branches of each are distributed on the same side of the midline on which its point of entry is found. The vessels which enter the pons at its cephalic end from the interpeduncular fossa and at its caudal extremity from the foramen caecum are especially numerous and large (fig. 1). Most of the former run in a straight line toward the fourth ventricle, which they approach at an angle of approximately 45 degrees with its floor. When near the surface, they bend sharply caudad to supply the structures along the median sulcus from the middle of the pontile part of the medial eminence as far back as the cephalic margin of the facial colliculus. The arteries do not diverge from near the midline during their course toward the fourth

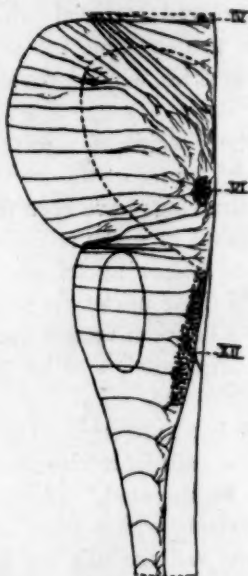


Fig. 1.—Diagrammatic representation of lateral view of median arteries of pons and medulla. In this figure and in figures 2 and 3, the various motor nuclei are represented by the stippling.

ventricle. There are also some small branches which enter just cephalad to these. They supply the remaining cephalic portion of the pons between the large vessels just described and the midbrain. They run more directly toward the ventricle, where they end in the medial eminence.

The median arteries, which enter at or near the foramen caecum, pass directly toward the floor of the fourth ventricle, some of them bending a little cephalad during their course (fig. 1). On nearing the surface, they bend sharply cephalad and are distributed to structures along the midline between the striae medullares and the anterior limit of the facial colliculus.

All the other arteries which enter along the median sulcus of the pons are spaced fairly evenly and pass with a slightly tortuous course toward the fourth ventricle, but do not extend to structures in its floor except to the anterior portion of the facial colliculus in some instances. Those entering the cephalic half of the sulcus basilaris bend in a caudal direction and parallel the vessels entering at the interpeduncular fossa when they approach them.

LATERAL ARTERIES OF PONS

The lateral portions of the pons and the corresponding parts of the fourth ventricle are supplied by numerous *arteriae laterales*, which vary

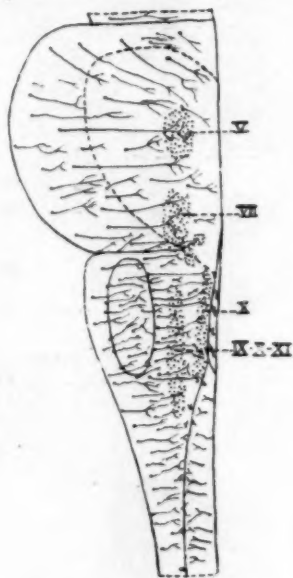


Fig. 2.—Diagrammatic representation of lateral view of lateral arteries of pons and medulla.

considerably in diameter and length but which are evenly distributed in its substance (fig. 3). Those near the interpeduncular fossa pass backward at about the same angle as those in the midline (fig. 2). Many of the larger ones, especially those in the middle third of the pons, form an arc with the convexity directed laterally in their course toward the fourth ventricle. The more laterally placed vessels converge somewhat toward the midline. Those entering the caudal end are directed cephalad, but in most instances not to the extent of being perpendicular to the surface of the pons at their point of entry. The largest of these enter along the groove between the pons and the medulla. The nuclei of the fifth, seventh and eighth nerves are in the portion of the pons supplied by the lateral arteries.

MEDIAN ARTERIES OF MEDULLA

The terminal branches of the median arteries which enter the anterior median fissure of the medulla supply the caudal portion of the floor of the fourth ventricle and in the closed portion of the medulla, the structures which are anterior to the central canal (fig. 1). They deviate little from the midline until the vicinity of the ventricle or canal is reached, where they break up into small branches. As in the pons, the branches from any single artery are practically all distributed entirely to one side of the midline (fig. 3). The nucleus of the hypoglossal nerve is included in the area supplied by these vessels. Throughout the pons and medulla,

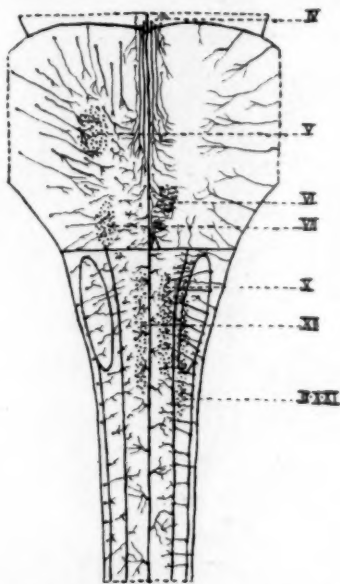


Fig. 3.—Diagrammatic representation of ventral view of arteries of pons and medulla.

distributary branches of arteries are especially large and numerous in the various nuclei. In the lower portions of the medulla the median arteries give off longer terminal branches and are also fewer in number, so that not only a wider area but more of the length of the medulla is supplied by each artery. The vessels in this part of the medulla usually bow somewhat in a cephalic direction during their course toward the central canal. The transition from short distributary branches to long ones and from a straight course to a curved one is gradual from the upper end of the medulla caudad. The arteries which enter the anterior median fissure are greater in diameter than any of the others which supply the medulla, with the exception in some cases of a number which enter along the anterior part of the posterior lateral sulci.

LATERAL ARTERIES OF MEDULLA

The lateral arteries which pierce the substance of the medulla along the posterior lateral sulcus follow the roots of the glossopharyngeal, vagus and accessory nerves to the nuclei. Caudal to the olive, these vessels are much shorter and smaller. A number of smaller lateral vessels enter the anterior lateral sulcus along which the root filaments of the hypoglossal nerve emerge. Their terminal branches are principally distributed in the portion of the inferior olivary nucleus adjacent to the pyramid. In addition, numerous considerably smaller arteries enter at evenly distributed points all over the surface of the medulla (figs.

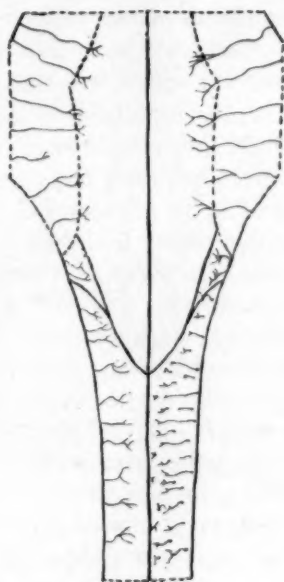


Fig. 4.—Diagrammatic representation of dorsal view of arteries of pons and medulla.

3 and 4). These vary greatly in size, many being mere capillaries; of course, they were not entered by the material injected. The course of each is nearly perpendicular to the surface and is directed toward the fourth ventricle or central canal, according to the level at which it is found. They supply the portions of the medulla lying between the vessels already described. This consists of most of the more superficial structures, including a large part of the pyramid and the most lateral portions of the caudal part of the fourth ventricle.

EFFECT OF SCLEROSIS ON BLOOD PRESSURE

In the past few decades, the advance of medicine and hygiene has brought arteriosclerosis to the fore as one of the most important diseases which prey on mankind. While occasionally found in the very young,

its incidence increases rapidly with age. As in the case of cancer, modern medicine has prolonged life and has thus provided this disease with many more persons who suffer from advanced cardiovascular or renal lesions accompanying it. Some evidence of the condition having been present is found at an extremely high percentage of autopsies, probably greater even than pulmonary tuberculosis. The distribution of the lesions shows marked variation in different persons.

Arteriosclerosis, together with the related renal and cardiac conditions, has been carefully investigated by many observers in an effort to determine the cause for the symptoms and the exact mechanism of their production. In a large proportion of the persons who become victims of this disease, the first intimation of the presence of the condition is the discovery of an elevated blood pressure. Even in these cases of so-called essential hypertension, careful search will usually reveal lesions of the small arteries in various organs, especially the kidneys.⁸

The reason there should be an elevated blood pressure has been the subject of much conjecture. At first it was suggested that the reduction in the stream bed in general by the thickening of the intima of the arteries might be the cause, but this theory was soon found untenable and had to be abandoned. Its relation to sclerosis of the arteries in the substance of the kidneys has been carefully studied.⁹ The resultant damage to renal tissue has been thought by some to result in retention of products that might cause an elevation of blood pressure by acting on the vasomotor center, or possibly by direct action on the musculature of the blood vessels. It does not seem probable that this is the cause, since marked hypertension may be present with little renal damage. A large proportion of patients having essential hypertension do not develop significant renal deficiency. In studying some of the products of protein metabolism, Major¹⁰ found that the guanidine compounds have power to cause elevation of blood pressure. Possibly there may be a variety of toxins having different origins that may produce this effect. Whether the same toxins are the ones that produce lesions in the intima of the arteries is yet to be discovered.

As stated by Bordley and Baker, the possibility that variations in the blood supply of the vasomotor center in the brain stem may cause alterations in general arterial pressure has seemed plausible to investigators for a number of years. Especial impetus was given this idea by the promulgation of "Cushing's Law" in 1901. Cushing observed that sys-

8. Fishberg, A. M.: Anatomical Findings in Essential Hypertension, *Arch. Int. Med.* **35**:650 (May) 1925.

9. Harpuder, Karl: Arteriosklerose, Schrumpfnieren und Blutdruck, *Deutsches Arch. f. klin. Med.* **129**:74, 1919.

10. Major, R. H.: Elevation in Blood Pressure Produced by Guanidine Compounds, *Bull. Johns Hopkins Hosp.* **35**:186, 1924.

temic blood pressure varies with the pressure exerted on the medulla. Previously, it had been noted that blood pressure rose when the blood supply to the brain was diminished.

In 1925, Starling¹¹ reported conclusions drawn from an ingenious experiment performed in the investigation of the regulation of arterial pressure. The head of a dog was provided with a blood supply separate from that supplying the main portion of the body. The rate of flow of this circulation could be varied at will. Records were made of the changes in pressure in the other portions of the body which were supplied by blood from the animal's own heart. It was found that the pressure in this circulation might be varied at will by altering the flow to the brain. A slight increase in the blood supplied to it caused a drop in blood pressure in the greater circulation. Likewise, a diminution of the flow in the brain caused an immediate rise in the blood supply of the body.

It has been noted by a number of observers¹² that ascent to high altitudes by aviators causes a rise in blood pressure, which falls on inhalation of oxygen.

Bordley and Baker¹ conceived the idea that a permanent diminution of blood flow in the vasomotor center such as might be produced by sclerosis of the arteries supplying it would cause a compensatory rise in blood pressure. In an attempt to find whether this might be true, they studied a series of twenty-four brains which had been preserved for various reasons. Many of them were from patients who had had cerebral hemorrhage. Systolic blood pressures of 165 or over were recorded in the histories of fourteen of their patients. Sclerosed vessels were found in the medulla in each of these. Little evidence of sclerosis was found in the other ten brains examined by them. Their study was made by examining sections from the level at which the vasomotor center is believed to be found.

ANALYSIS OF CASES

In making this study, I have selected brains removed at autopsies performed during the past year which seemed likely to provide evidence bearing on the problem that was being investigated. The series includes eighteen brains from patients in whom hypertrophy of the left ventricle of the heart, without valvular lesions, was found at necropsy. During life, fourteen of these patients had had systolic blood pressures of 170 or over as shown in the accompanying table. The diastolic pressure in each patient, except one, was over 95. Of the four remaining patients,

11. Starling, E. H.: The Physiological Factors in Hyperpiesia, *Brit. M. J.* 2:1163, 1925.

12. Grossman, M.: Ueber den Blutdruck im Hochgebirge, *Ztschr. f. klin. Med.* 102:86, 1926. Loewy, A.: Ein Beitrag zur Entstehung von Hypertonien, *Klin. Wchnschr.* 4:829, 1925.

Summary of Data of Patients Studied

Patients With Arteriosclerosis, Hypertrophy of Heart, and Hypertension				Distribution of Arteriosclerosis		Arteriosclerosis in Medulla Base of Brain	Sclerosis in Arteries at Base of Brain	Changes in the Kidneys	Cause of Death
No.	Age	Blood Pressure	Size of Heart	Mild	Severe				
1	41	184/96 to more than 300	Twice normal	Kl, H, Sp, Ao	Very slight	Marked	Numerous scars	General arteriosclerosis; cerebral hemorrhage
2	63	220/150	About twice normal	Kl, H, Ao	Moderate severity	Extreme	Many scars	General arteriosclerosis; cerebral hemorrhage
3	51	About 80; marked decomposition on entry	Extremely large	Kl, H, Li	Sp, Ao	None	Moderate	Few scars	General arteriosclerosis; decomposition
4	76	125/90; marked decomposition on entry	Between 2 and 3 times normal	Kl, H, Sp, Ao, Pa, Lu	None	Much	Many scars	General arteriosclerosis; decomposition
5	63	116/64; marked decomposition on entry	Twice normal	Li	Kl, H, Sp, Ao, Pa	None	Slight	Number of scars	General arteriosclerosis; decomposition
6	67	132/78 to more than 225	Very large	Kl, H, Lu	Ao	None	Much	Marked scarring	General arteriosclerosis; decomposition
7	82	220/76	Moderately large	H	Kl, Sp, Ao, Ad	Slight	Moderate	Many scars	General arteriosclerosis; decomposition
8	58	180/110 to 210/120	Twice normal	Li	Kl, H, Ao, Pa	Slight	Much	Chronic nephritis	General arteriosclerosis; chronic nephritis; cerebral hemorrhage
9	62	150/90 to 300/120	Very large	Kl, H, Sp, Ao, Pa	Moderate severity	Marked	Much scarring	General arteriosclerosis; coronary thrombosis with necrosis of heart muscle
10	56	206/95	1½ times normal size	Kl, H, Sp, Ao, Pa	Little	Extreme	Few scars	General arteriosclerosis; cerebral hemorrhage
11	23	175/95 to 195/105	Marked hypertrophy	H, Sp	Kl	None	None	Subacute nephritis	Late subacute nephritis; uremia
12	70	160/118 to 194/108	Moderately large	H, Pa	Kl, Sp, Ao, Lu	Moderate	Marked	Some scarring	General arteriosclerosis; decomposition
13	71	120/58 to 190/110	Moderately large	Lu	Kl, H, Ao	None	Marked	Many scars	General arteriosclerosis; coronary arteriosclerosis; coronary sclerosis with necrosis of myocardium; diabetes
14	82	154/86 to 184/100	1½ times normal size	Kl, Sp, Ao, Pa, Li	None	Slight	Numerous scars	General arteriosclerosis; decomposition
15	61	More than 170 systolic	1½ times normal size	Kl	H, Ao	None	Very slight	Few scars	General arteriosclerosis; cardiac noma; prostate
16	40	176/98	Moderately large	H, Ao, Ad	Kl, Sp, Pa	Slight	Moderate	Chronic nephritis	General arteriosclerosis; chronic glomerular nephritis; uremia
17	64	110/90 to 170/94	Slight enlargement	Ad	Kl, Sp, Ao	None	Moderate	Few scars	General arteriosclerosis; multiple softening of brain; pellagra

18	60	90/65 to 145/80	Hypertrophy of left ventricle	Ao	Kl, H, Sp	None	Slight	Number of scars	General arteriosclerosis; atrophic cirrhosis of the liver
Patients with Generalized Arteriosclerosis Without Hypertrophy of Heart									
19	53	130/80	Normal	H	Kl, Sp, Ao	None	None	None	General arteriosclerosis; diabetes
20	45	125/70	Normal	Kl, Sp, Ao	H	None	Moderate	None	General arteriosclerosis; chronic alcoholism
21	72	Not recorded	Enlarged to right only	H	Kl, Sp, Ao	None	None	Some scars	Chronic endocarditis with stenosis of mitral valve; general arteriosclerosis
Patients Without Generalized Arteriosclerosis									
22	56	90/64 to 152/108	Slightly large	Ao	Sp	None	Little	Few scars	Carcinoma of the colon
23	40	155/68	Normal	Kl, H, Sp	None	Slight	Few scars	Carcinoma of the rectum
24	50	130/80 to 140/90	Small	Kl, Ao	None	Slight	None	Carcinoma of the pancreas
25	24	122/76 to 138/88	Small	Ao	None	None	None	Chronic syphilis of the liver; thrombosis of the portal vein
26	66	138/58	Normal	Sp	Kl, Ao	None	Moderate	Few scars	Carcinoma of the stomach
27	49	124/68	Small	Ao	None	None	Few small scars	Carcinoma of the esophagus
28	52	120/70	Normal	Ao	Kl	None	Slight	Some scars	Atrophic cirrhosis of the liver
29	29	Not recorded	Normal	None	None	Few scars	Stenosis of bronchus with bronchiectasis
30	56	118/76	Small	Kl, H, Ao	None	None	Few scars	Lymphosarcoma of the intestine
31	58	118/90	Normal	Kl, Sp, Ao, Ll	None	Moderate	Small tubercles	Acute general tuberculosis
32	49	80/50 to 110/90	Normal	Sp, Ao	None	Moderate	Few scars	Subacute yellow atrophy of the liver
33	33	110/75	Normal	Ao	None	None	None	Chronic ulcer of the stomach; gastrectomy
34	43	100/76	Normal	Kl, H, Ao, Sp	None	None	Few scars	Tuberculosis of the lungs
35	29	94/54	Normal	Ao	None	None	Few scars	Myelocytic leukemia; cerebral hemorrhage
36	54	60/42 to 82/70	Small	Kl, Sp, Ao	None	Moderate	Some scars	Addison's disease*

* In the table, the abbreviations used are: Kl, kidney; H, heart; Ao, aorta; Ll, liver; Lu, lung; Sp, spleen; Ad, adrenal; Pa, pancreas.

three had marked hypertrophy of the heart but were seen only in a state of advanced cardiac decompensation. It is reasonable to assume that the failure of the heart in each of these cases had been preceded by marked continued hypertension. In the remaining case, the blood pressure had never exceeded 145 systolic, but a definite concentric hypertrophy of the left ventricle was discovered at autopsy.

Four of these eighteen patients were less than 50 years of age; twelve were more than 60.

The study of the relation of the sclerosis of the arteries supplying the vasomotor center to hypertension has consisted of examining the



Fig. 5.—Stereoscopic photograph of anteroposterior view of arteries of pons and medulla.

brains from these eighteen patients by the methods which have already been described.

DATA ON CASES OF GENERAL ARTERIOSCLEROSIS

The autopsies of seventeen patients showing hypertrophy of the left ventricle of the heart revealed such widespread arteriosclerosis that the condition was described as generalized.

DATA ON CASES OF NEPHRITIS

Three of the eighteen patients had had symptoms and manifestations indicating renal damage during life. At autopsy, sufficient lesions were found in the kidneys to class them with those showing chronic nephritis.

All three of the patients had high blood pressure. Two died of uremia, and one of cerebral hemorrhage. Sections of the medulla from the two with general arteriosclerosis showed occasional slightly thickening vessels. The third patient, although the blood pressure had gone up to 195 systolic, had neither general arterial disease nor any lesions in the blood vessels of the medulla.

DATA ON CEREBRAL HEMORRHAGE

Five of the brains which were studied contained large destructive hemorrhages. In three of them, the principal damage occurred in the



Fig. 6.—Stereoscopic photograph of lateral view of arteries of pons and medulla.

basal ganglions. In the others, the hemorrhage originated in the upper portion of the pons and caused marked damage to the structures in the floor of the fourth ventricle. One of the patients with cerebral hemorrhage had myelocytic leukemia. Elevation of blood pressure or hypertrophy of the heart was not present in this case; neither was there any sclerosis of the small arteries in the brain. The other four patients had marked hypertension, general arteriosclerosis, and great thickening of the wall of the left ventricle of the heart. Chronic nephritis was also present in one of these patients. One of the brains showed slight thickening of only a few vessels in medulla. In the other three, there was sclerosis up to a moderately severe degree. A varying amount of

sclerosis was also found in the other parts of the brain in these cases. The frequency of diseased arteries in the brain stem in cerebral hemorrhage explains the frequent finding of arterial lesions in the instances of high blood pressure studied by Bordley and Baker, because eight out of their fourteen patients with hypertension had died from hemorrhage into the brain.

ORIGIN OF CEREBRAL HEMORRHAGES

Serial sections were made from one of the brains showing multiple hemorrhages in the pons in order to trace the lesions of the vessels from which some of the smaller hemorrhages had occurred. The walls of these vessels were somewhat thickened throughout. On approaching the site of a hemorrhage, the vessels began to show signs of degeneration. The nuclei of the cells in the wall of a vessel ceased to stain. Finally, a short portion of the wall of the vessel appeared to be completely dissolved, and its sheath in this area was distended with blood. Aneurysms were not found, nor was the lumen in the degenerated areas greater in diameter than elsewhere. My observations in this regard confirm those of Westphal and Bär¹³ in regard to the arterial changes in cerebral hemorrhage.

FREQUENCY OF HIGH BLOOD PRESSURE IN PATIENTS WITH ARTERIAL DISEASE AT THE BASE OF THE BRAIN

A varying amount of sclerosis of the large arteries at the base of the brain was found in twenty-five cases. In only fifteen was there any evidence of elevated blood pressure as shown by the history or at autopsy. This lack of correlation is in accord with the previous observations of Woltman.¹⁴

FREQUENCY OF ARTERIAL DISEASE OF THE BRAIN STEM IN HIGH BLOOD PRESSURE

On examining sections of the medulla from the eighteen patients showing evidence of having had hypertension, I was unable to find thickened vessels in ten. In four others, the evidence of sclerosis was slight. In these four, only occasional vessels showed any evidence of thickening. Four brains showed varying degrees of arteriosclerosis up to moderately severe. Three of these were from patients who had had cerebral hemorrhage. Each of these four patients had had systolic blood pressures of 195 or over. In three other patients having blood pressures of over 195, with hypertrophy of the heart and without valvular lesions, I was unable to find thickened vessels in the medulla.

13. Westphal and Bär: Ueber die Entstehung des Schlaganfalles, *Deutsches Arch. f. klin. Med.* **151**:1, 1926.

14. Woltman, H. W.: Cerebrospinal Arteriosclerosis, *Minnesota Med.* **5**:102, 1922.

In this series, an invariable relationship between the condition of the arteries in the medulla in the region of the vasomotor center and the blood pressure could not be demonstrated. More than half the cases in which there was evidence of an elevated blood pressure did not show sclerosis of the vessels in the medulla. However, patients who had thickened arteries in this part of the brain without an accompanying elevation of blood pressure were not found, but the series is too small to justify the prediction that this will not be found.

If a diminution of the blood supply to the vasomotor center is the cause of high blood pressure in hypertension, it would seem that in at least a considerable number of cases this is accomplished by other means than a permanent narrowing of the lumen of the arteries. It is of course possible that the unknown agent which is responsible for the condition causes a constriction of the vessels, although this is a purely theoretical assumption.

The present investigation does not disprove the contention that interference with the blood supply to the vasomotor center is the cause of high blood pressure, but it shows that this interference, if it does exist, is not due to gross anatomic lesions in the blood vessels.

CHANGES IN THE SPECIMENS THAT WERE INJECTED

The specimens that were injected showed a few moderately tortuous vessels in the medulla of the brains of patients who had had sclerosis. There was perhaps a moderate reduction in the average diameter of the vessels, and a few showed slight irregularities in the lumen. However, noticeable differences in the appearance of the injected vessels in cases showing sclerosis from those in which thickened vessels were not found on examination of sections were not seen. Neither could any definite effect on the completeness of the injection be detected.

CONCLUSIONS

1. A description is given of the normal distribution of the arteries in the substance of the pons and of the medulla.
2. Examination of the medulla in eighteen cases of hypertension showed slight to moderately severe sclerosis of the arteries in eight.
3. The most marked sclerosis of these vessels was noted in patients with cerebral hemorrhage. In all of these, the systolic blood pressure had been over 200.
4. Specimens of the pons and medulla which were injected did not show noticeable tortuosity or narrowing or irregularity of the lumen of the arteries in brains showing sclerosis of the vessels in these parts.
5. If the high blood pressure is due to a lack of blood supply to the vasomotor center, it is evident from the studies that this abnormal condition is not caused by any demonstrable anatomic changes in the arteries of this region.

THE REACTION TO OILS AND FATS IN THE LUNG *

HENRY PINKERTON, M.D.

BOSTON

A report has been made¹ of six instances in which oily substances accidentally entered the lungs of infants, and the reaction on the part of the lung tissue was shown to be primarily the ingestion of the oil by large mononuclear phagocytes, with subsequent giant cell formation and fibrosis. A careful study of the staining reactions, solubility and other characteristics of the material in the lungs of these infants showed that several different kinds of oil were present.

In this report, note was made of the fact that roentgenologists have used iodized oils, extensively and with apparent impunity, for the purpose of outlining the bronchial tree. Because of the severe damage to the lung tissue in the cases reported, it was difficult to believe that this diagnostic procedure could be entirely without ill effect, and it was thought advisable to determine experimentally the reaction of the lung tissue to the various oils. These experiments have brought out surprising difference in the reactions to the various oils of vegetable, animal and mineral origin.

THE REACTION TO THE VEGETABLE OILS

Iodized Vegetable Oils.—Two proprietary products (lipiodol and iodipin) were investigated. These were said to be, respectively, poppy seed oil and sesame oil, both containing 40 per cent of iodine. No essential differences were found in the reactions to these two oils, and they may be considered together.

Five puppies and nine rabbits were injected intratracheally with these oils, the former with 10 cc. each and the latter with from 3 to 5 cc. each. The oils were sterile as far as could be determined by cultural tests, and the procedure was carried out aseptically. The puppies were etherized, but, in the case of the rabbits, the introduction was carried out readily without anesthesia. The entrance of the oil into the lungs was confirmed by taking roentgenograms shortly after the injection. These pictures showed that the oil was distributed unequally between the two lungs, the right receiving by far the larger

* From the Department of Pathology, Harvard University School of Medicine, and the Pathological Laboratory, Peter Bent Brigham Hospital, Boston.

1. Pinkerton, H.: Oils and Fats—Their Entrance Into and Fate in the Lungs of Infants and Children, *Am. J. Dis. Child.* **33**:259 (Feb.) 1927.

portion, although the animals were always placed in a symmetrical position on their backs.

One of the puppies died four days after the injection, the cause of death being an extensive intussusception of the ileum into the cecum. The right lung (shown by the roentgen ray to contain the greater part of the oil) was found at autopsy to be definitely reddened. Frozen sections showed that the majority of the alveoli were filled with a single large mass of oil. The oil was not emulsified, and none of it was intracellular. Paraffin sections (eosin-methylene blue stain) showed normal lung tissue, except for slight congestion, the oil having been dissolved out by the alcohol and xylene.

Three of the puppies developed bronchitis on the third or fourth day after injection, and died two, sixteen and twenty-one days later. There did not seem to be a good reason for believing that the introduction of the oil was responsible for the development of the bronchitis in these animals, although the etherization may have been a factor. The lungs of these dogs showed the typical picture of infectious bronchitis with patchy pneumonic consolidation of the lungs. In the most acute case, the exudate was composed almost entirely of polymorphonuclears, and the oil was found lying free in the alveoli—never within the leukocytes. In the more chronic cases, a considerable number of large mononuclear leukocytes were present in the lungs of the animals, as would be expected in such a long continued pulmonary infection. Quite a few of these mononuclears had ingested small droplets of oil, but this was considered an incidental phenomenon, and not due directly to the presence of the oil, since no such reaction was found in the lungs of those animals which remained free from infection. In a few instances, the epithelial cells lining the bronchioles contained many minute droplets which stained red with scharlach r. This was an inconstant occurrence, and the adjacent bronchioles were entirely free from any such appearance, although their lumina contained an equal amount of oil.

The fifth puppy was isolated from the third day, and kept under excellent hygienic surroundings. This animal remained well, and gained weight rapidly. By the end of the third month, there was considerable diminution in the density of the roentgen-ray shadow, and after five and one-half months, there was only a slight questionable haziness. The animal was then chloroformed, and the lungs were carefully studied. Grossly, their appearance was entirely normal. Frozen sections showed, in a few areas, an occasional alveolus filled with two or three large droplets of oil. This oil was not emulsified, and there was no cellular reaction to it. In paraffin sections, an occasional bronchiole was found partly filled with a mucinous secretion, in which desquamated epithelial cells were present, and a rare bronchiole was definitely dilated, but other changes were not seen.

The nine rabbits injected with these iodized oils remained well, and were killed 8, 16, 25, 33 (two), 45, 60 and 90 (two) days after injection. In seven of these animals, the lungs appeared grossly normal. Microscopically, the oil was present in the alveoli in large rounded masses, but no cellular reaction to it was discoverable (fig. 1). In paraffin sections, stained with eosin-methylene-blue, there was nothing to distinguish these lungs from normal lungs, except the presence of a rare large mononuclear in the alveoli.

Each of the lungs of the other two rabbits, killed twenty-five and thirty-three days after injection, showed two or three small abscesses, the largest of which was 4 mm. in diameter. These abscesses were usually subpleural, projecting outward from the surface as small nodules, which, when punctured, yielded a soft grayish-white puriform material. Microscopically, the alveoli in the central portions of these lesions were still discernible, but their walls were poorly stained, and their lumina contained moderate numbers of polymorphonuclears. The abscesses were surrounded by fairly definite connective tissue walls. The immediately adjoining alveoli contained a few oil-laden large mononuclears. The blood vessels in these areas showed striking endothelial proliferation and considerable infiltration of their walls with polymorphonuclears, lymphocytes and large mononuclears. The lung tissue in these two cases was saturated with oil, but, except in the walls of these abscesses, there was no cellular reaction to it. These abscesses, because of their inconstant appearance, were thought not to be a reaction to the oil itself. It seemed probable that the obstruction of the smaller bronchioles by the oil was an important factor in their production. The heavy sticky nature of these iodized oils would favor such a process.

The lungs in these rabbits and dogs were the only organs that showed any changes. No oil could be demonstrated in the bronchial lymph nodes (by scharlach r stained frozen sections).

Olive Oil.—Four rabbits, injected in a similar manner with olive oil, remained well; they were killed six, eighteen, twenty-eight and fifty-four days after the injections were made. The lungs were grossly normal in each instance. Microscopically, practically the same absence of cellular response was found as in the case of the iodized vegetable oils. There was, however, a slight but definite large mononuclear reaction, which was most marked in the rabbit killed six days after injection. Even in this case, however, there were rarely more than two or three oil-laden phagocytes in a single alveolus, even in the areas in which the alveoli were shown by frozen section to be filled with oil; most of the oil was not emulsified.

Chaulmoogra Oil.—Four rabbits injected with from 3 to 4 cc. each of this oil died within twelve hours. The lungs were deep red

and greatly enlarged. Microscopically, the alveoli were filled with serum and fibrin, with a few polymorphonuclears and large mononuclears. The alveolar walls were poorly stained and eosinophilic.

By reducing the amount injected to 2 cc., two rabbits were kept alive for ten and twenty-two days. The lungs of these rabbits showed large areas of necrosis, surrounded by connective tissue walls. In the walls of these necrotic areas, there was much fibrosis and giant cell formation around the masses of oil. Extraordinary proliferative changes were seen in the epithelium of these lungs. These changes were comparable to those produced by lard oil, which will be described below.

This oil apparently contains a strong chemical irritant of some sort, which produces acute necrosis of the lung tissue. The nature of this irritant will be discussed later.

THE REACTION TO THE ANIMAL OILS

Cod Liver Oil.—Seven rabbits were injected with this oil, from 4 to 5 cc. being given to each animal. The oil was sterilized by autoclaving, and cultures did not show growth.

One rabbit died eighteen hours after the injection. The lung tissue was found to be completely saturated with oil, and it was obvious that this rabbit had been practically drowned by the oil. Microscopically, the alveoli did not contain the acute serofibrinous exudate which was noted in the animals that died shortly after the injection of chaulmoogra oil.

The remaining six rabbits remained well and were killed 15, 21, 38, 50 (two) and 110 days after injection. In each case, those portions of the lung which the oil had entered (usually the greater portion of the right and from one third to one half of the left lung) were found to be markedly solidified and yellowish, both externally and on section. The degree of firmness was nearly as great in the rabbit killed after fifteen days as in the rabbits killed after fifty days, but in the case of the rabbit permitted to live 110 days, the right lung was found to be markedly contracted and cicatrized. In this case, the spine was curved markedly to the left, so that the right cavity of the chest was considerably larger than the left. The right cavity contained the heart (drawn over by the contracting tissue of the lung) and the small, firm right lung, completely hidden from view by fatty tissue, which appeared to have extended from the peribronchial region and completely filled the pleural cavity. All of these structures were firmly adherent to the wall of the chest, so that the lung was dissected out with great difficulty.

Microscopically, the lung tissue from these cases had a remarkable appearance (figs. 2, 3, 4 and 5). In many areas, each alveolus contained a single large irregular mass of oil surrounded by enormous

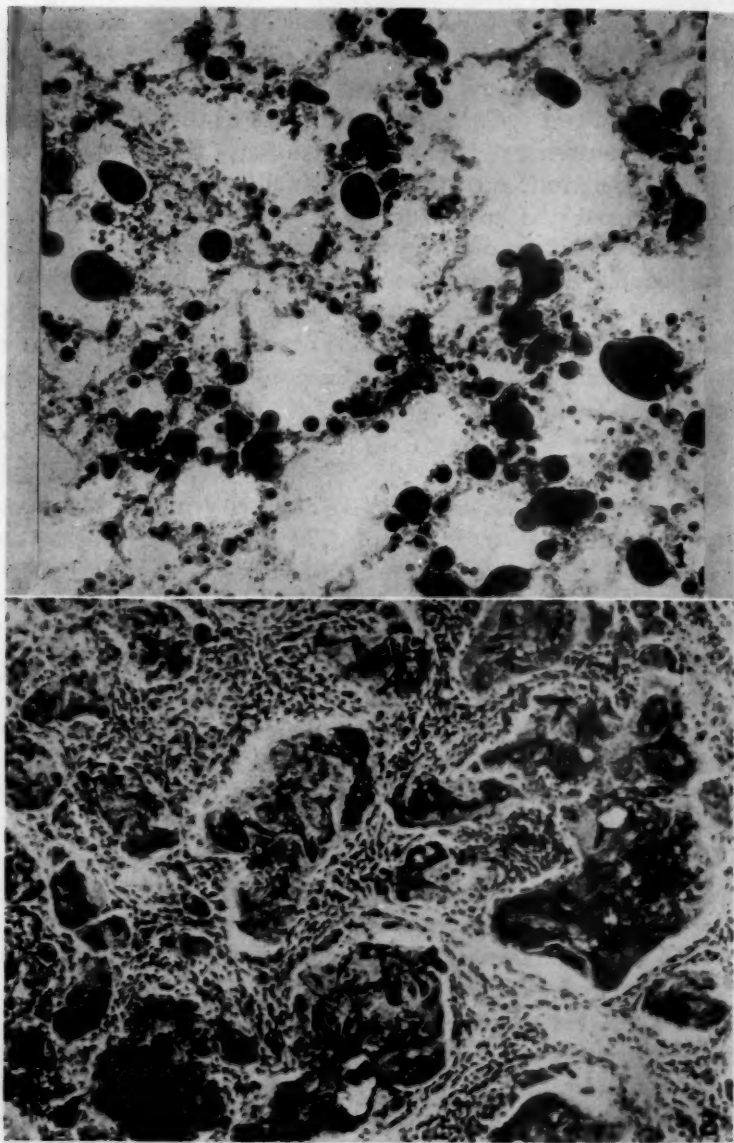


Fig. 1.—Iodized poppy seed oil in the lung of a rabbit shown in frozen section, stained by scharlach r and hematoxylin; duration, sixty days. The oil was not emulsified. The lung tissue was essentially normal.

Fig. 2.—Cod liver oil in the lung of a rabbit shown in frozen section, stained by scharlach r and hematoxylin; duration, twenty-one days. The alveoli are filled with shaggy masses of oil and much fibrosis of the alveolar walls is seen.

giant cells. These masses of oil showed a curious shredded appearance and had assumed bizarre, spider-like shapes. The extremely large size of the giant cells seemed to be due to their effort to hold a substance which was continually sending out long pseudopod-like processes. Both in the alveoli and in the alveolar walls, there were also present many single large mononuclear phagocytes containing smaller masses of oil. The masses of oil within many of the large mononuclear and giant cells showed irregular, indefinite outlines, and the surrounding cytoplasm showed a diffuse reddish staining with scharlach r, suggesting that the edges of the masses of oil were being digested by the cell enzymes. This observation holds true for all of the animal oils investigated. The alveolar walls were greatly thickened, and there was much newly formed connective tissue. In addition to the large mononuclear phagocytes in this connective tissue, there was a heavy infiltration with lymphocytes and eosinophils and a few polymorphonuclears.

In the case of the rabbit which was allowed to live 110 days, there was much more complete obliteration of the architecture of the lungs than in the animals in the earlier cases. Many areas of necrosis were also present; they were composed of a central core of eosinophilic material in which faint outlines of necrotic cells could be made out, together with pyknotic nuclei and a few polymorphonuclears. These areas were surrounded by a zone of oil-laden large mononuclears and giant cells, and still farther out by a wall of dense connective tissue, heavily infiltrated with lymphocytes. The histology in many areas bore a superficial resemblance to that of tuberculosis.

There are several peculiarities in the staining reactions of cod liver oil which are of interest. After fixation in either Zenker's solution or solution of formaldehyde, the oil in the tissue of the lung is not dissolved out by the fat solvents employed in the ordinary method of paraffin embedding. (This fact was pointed out in connection with the human cases of cod liver oil aspiration previously reported.) This insolubility in xylene and other fat solvents is in contrast to the fact that cod liver oil as such is readily dissolved by these solvents. In the lungs of the rabbits described above, the oil was readily visible in paraffin sections, and with eosin-methylene blue stain showed various staining reactions, varying from yellow and green to bright pink. The globular masses were practically always pale yellow or green, while the irregular shreddy masses of oil were stained a reddish pink.

Another property of cod liver oil in the lung (also, but less strikingly, of rabbit fat) is its great affinity for carbol fuchsin. Stained by the Ziehl-Nelson method, it retains this stain fully as tenaciously as does the tubercle bacillus, and excellent contrast stains can be made in this way. Cod liver oil acquires this property of being acid fast only by a fairly prolonged stay in the lung, for oil which has been in the

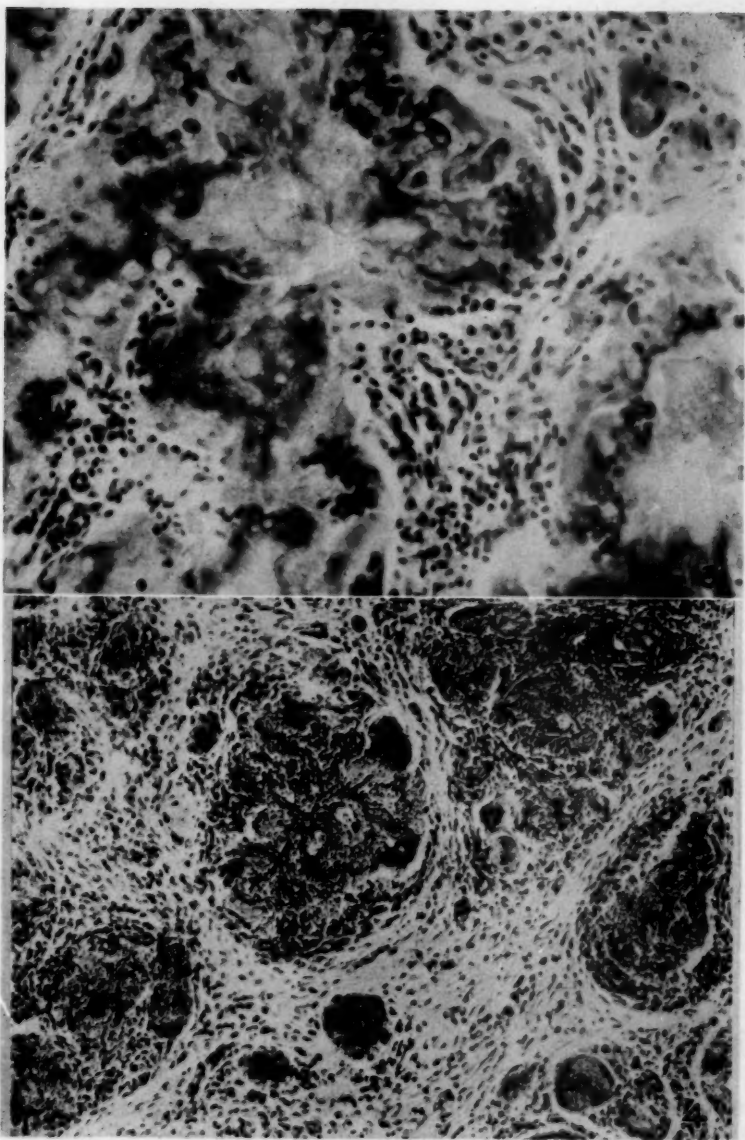


Fig. 3.—Cod liver oil in the lung of a rabbit from the same slide as figure 2 showing enormous giant cells containing shreddy masses of oil.

Fig. 4.—Cod liver oil in the lung of a rabbit, shown in frozen section, stained by scharlach r and hematoxylin; duration, thirty-eight days.

alveoli for only a few hours and oil in the alveolar wall capillaries (introduced by way of the ear vein, the rabbit dying in six hours) does not retain the carbol fuchsin.

On examining the bronchial lymph nodes, a considerable amount of cod liver oil was found. This oil was contained in large mononuclear phagocytes (never in giant cells, presumably because they are too large to pass along the lymph channels) and most of it was situated in a marginal position around the lymph follicles (fig. 6). Oil was not found in the spleen or in the other organs. (In one of the human cases previously reported, considerable amounts of mineral oil were present in the spleen.)

Milk Fat.—The reaction to milk fat is somewhat similar, but considerably less striking than that to cod liver oil. Two rabbits were injected with butter and one with heavy cream. They were killed twenty-one, thirty-eight and sixty-five days after injection. In each case, the portions of the lung reached by the fat could be easily distinguished grossly by their increased firmness and grayish color on section. Microscopically, the alveoli contained large numbers of mononuclear phagocytes and quite a few oil-laden giant cells, but the giant cells were much less numerous and smaller than in the case of cod liver oil. The alveolar walls in many areas showed a diffuse increase in connective tissue, and many small areas of solid connective tissue (from 1 to 2 mm. in diameter) were present. In this connective tissue were many oil-laden giant cells and mononuclears, as well as a considerable proportion of eosinophils and polymorphonuclears. In many areas, the cytoplasm of the fibroblasts appeared to contain fine droplets of oil. The bronchial lymph nodes here also showed a few collections of oil-laden phagocytes.

Rabbit Fat.—One rabbit was injected with 3 cc. of rabbit fat; this was obtained by extracting the retroperitoneal adipose tissue of a rabbit with chloroform and then evaporating the solvent.

This rabbit continued to be in good health and was killed twenty-five days after the injection. Grossly, there was marked consolidation of both lower lobes and of the right middle lobe. Microscopically, there was a moderate diffuse fibrosis of the alveolar walls, and the alveoli contained many large giant cells which inclosed masses of fatty material. A considerable portion of this fat was visible in paraffin sections, staining pink with eosin. The fatty material in several of the giant cells had a striated appearance, the striations radiating from the centers of the masses to their edges. As mentioned before, the greater part of this insoluble fatty material was found to be acid fast.

The bronchial epithelium showed some hyperplasia, and small bronchioles lined with several rows of tall columnar epithelium were conspicuous throughout the sections.

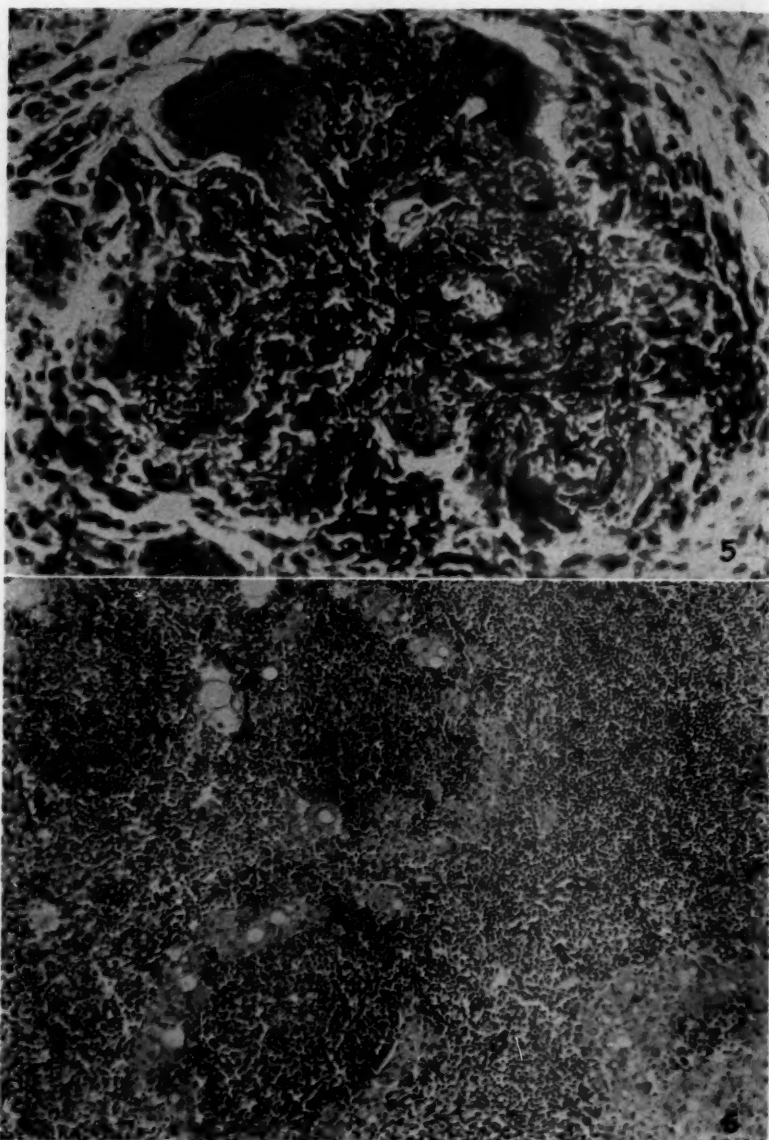


Fig. 5.—Cod liver oil in the lung of a rabbit shown in higher magnification of the central portion of the field as in figure 4; shreddy masses of oil surrounded by giant cells.

Fig. 6.—Cod liver oil in large mononuclear cells in the bronchial lymph node shown as stained by eosin-methylene blue.

The most interesting feature of the reaction to rabbit fat was the formation of what appeared to be small islands of normal fatty tissue in the lung. This appearance was particularly striking around the arteries and veins, practically all of which were surrounded by wide zones of contiguous "signet ring" cells (fig. 7). A similar appearance was noted about many of the bronchioles, and, more rarely, the fat in the alveoli appeared to have been "organized" in the same way. The fat in these islands was dissolved out in the process of paraffin embedding, like that of normal adipose tissue. In fact, these islands differed from normal fatty tissue only in that there was somewhat more variation in the size of the individual fat-containing cells.

In attempting to work out the sequences leading to this curious end-result, it appeared that the masses of fat were first surrounded by cells which, from their appearance, might be endothelial phagocytes or young fibroblasts. These cells then formed syncytial masses which entirely surrounded the large masses of fat. The cytoplasm of these multinucleated cells then appeared to subdivide these masses into several smaller portions of convenient size, and each unit was eventually composed of a spherical mass of fat, surrounded by a narrow rim of cytoplasm, with a peripherally situated nucleus. In other cases, fibroblasts appeared to be growing into the masses of fat and "organizing" them, without previous giant cell formation.

Lard Oil.—Six rabbits, each injected with 4 cc. of lard oil (an amount readily tolerated in the case of the other animal oils), were found dead within twenty-four hours from the time of injection. Grossly, the involved portions of the lungs in these cases were enlarged, red and edematous. Microscopically, the alveoli were filled with serum and fibrin, with a few polymorphonuclears, lymphocytes and large mononuclears, together with many large and small globules of oil. The appearance was that of a sudden acute inflammation produced by some irritating chemical substance.

At first it was thought that the oil must have become rancid; but when a fresh supply was used, it was found to have the same effect on two rabbits.

By reducing the amount to from 2 to 2.5 cc., successful injections were made into five rabbits. Three of these rabbits died six, nine and twenty-five days after the injection, while the other two were killed in a moribund condition on the thirty-first and thirty-third days. Grossly, the lungs of all of these animals were enlarged and congested, and firm opaque nodules (from 2 to 20 mm. in diameter) were seen and palpated throughout the tissue of the lung. There were numerous pleural adhesions where these nodules extended to the pleural surface, and in one case the pleural cavity contained an opaque, creamy liquid

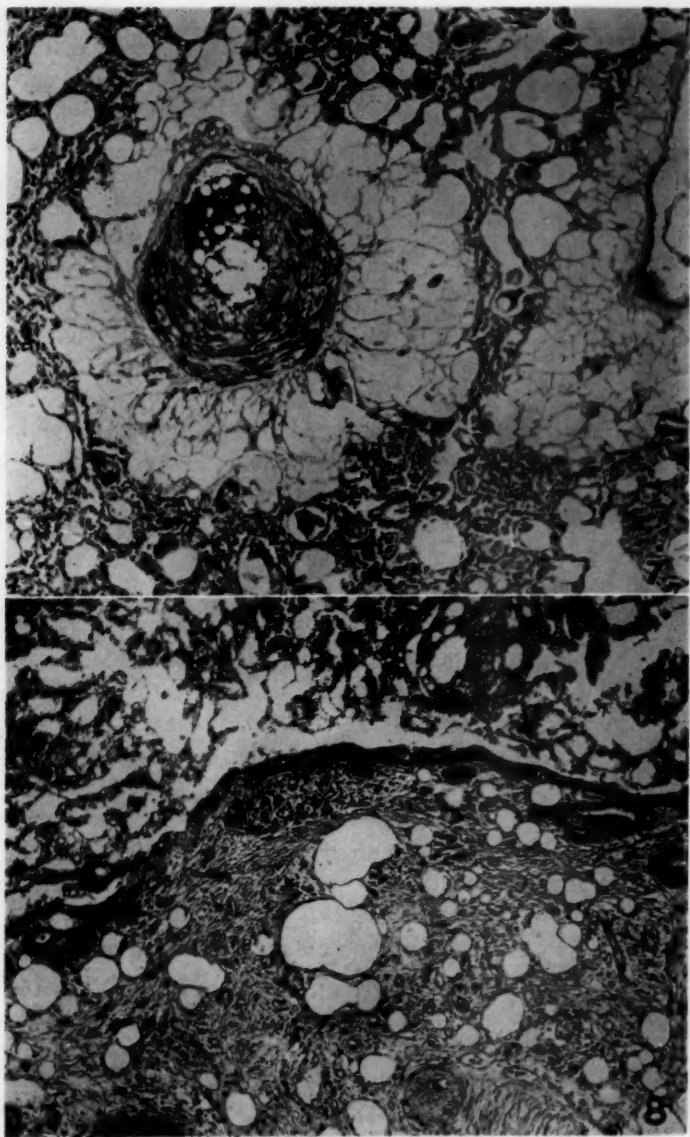


Fig. 7.—Rabbit fat in the lung of a rabbit, stained by eosin-methylene blue, showing giant cell formation and periarterial and perivenous storage zones.

Fig. 8.—Lard oil in the lung of a rabbit, stained by eosin-methylene blue; necrotic area with newly formed epithelial lining and fibrosis and giant cell formation.

which microscopically contained large mononuclears, eosinophils, a few polymorphonuclears and many globules of oil. Cultures of this liquid remained sterile.

On section, many of these nodules were seen to contain a thick, caseous material in their centers, but the smaller ones (less than 5 mm. in diameter) were composed entirely of firm fibrous tissue. Many of these necrotic areas had somewhat the gross appearance of bronchiectatic abscesses, but this was not true of the microscopic appearance, for their centers contained an eosinophilic material in which the outlines of alveoli could be faintly made out, together with pyknotic nuclear fragments and many necrotic wandering cells. The necrotic lung tissue had much the appearance of an area of tuberculous bronchopneumonia.

In other areas there was a striking giant cell formation and fibrosis similar to that produced by the other animal oils. This reaction was equal in intensity to that produced by cod liver oil, and in some areas the oil assumed the same shreddy appearance within giant cells which has been described in the case of cod liver oil. Much of this oil was also visible in paraffin sections and showed the same variegated staining as cod liver oil. The newly formed connective tissue contained much finely divided oil, many of the minute droplets apparently being within the cytoplasm of the fibroblasts.

Interesting proliferative changes occurred in the epithelium of the lungs injected with this oil (figs. 8, 9 and 10). In many areas, the epithelium appeared not only to be growing into and filling up the lumens of the bronchioles, but also to be growing outward into the surrounding tissue in an almost invasive manner. In some places also small irregular islands of epithelium were present which were not in relation to the bronchioles, but which appeared to have originated in the alveolar epithelium. This neoplastic-like activity of the epithelium was seen most strikingly in the lungs of the rabbit which died nine days after the injections had been made, but it was well marked in the five animals injected with lard oil. Furthermore, in many instances the epithelium had partially, and in a few instances completely, lined the large areas of necrotic lung tissue already described. One area of necrotic but still recognizable lung tissue, 1 cm. in diameter, had thus become completely surrounded by a wall of irregular newly formed epithelium. It thus seemed impossible to escape the conclusion that the epithelium plays a part in the repair of a cavity produced by sudden necrosis of an area of lung tissue.

Entirely similar epithelial changes were obtained with chaulmoogra oil, as already stated.

Reaction to Mineral Oil.—Six rabbits were injected with mineral oil, from 4 to 5 cc. being used. Five of these rabbits remained well, and were killed 7, 12, 28, 56 and 90 days after the injections. The

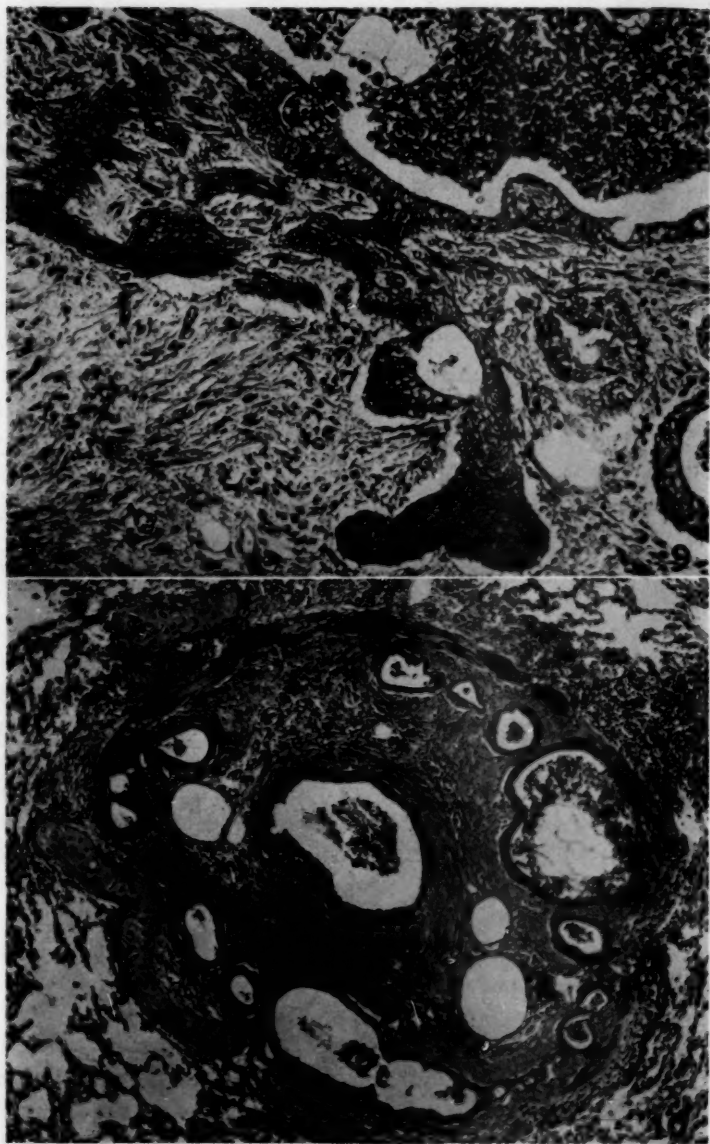


Fig. 9.—Lard oil in the lung of a rabbit, stained by eosin-methylene blue, showing neoplastic-like epithelial proliferation following rapid necrosis.

Fig. 10.—Chaulmoogra oil in the lung of a rabbit, stained by eosin-methylene blue, showing recanalization of a bronchus.

sixth rabbit died 115 days after the injections with paralysis of the hind legs and extreme emaciation.

Grossly, the lungs in each case showed marked consolidation of the involved portions, but the degree of firmness increased progressively with the length of time the oil had remained in the lungs.

Microscopically, the appearance of the lung tissue in these areas is readily distinguished from that produced by the animal oils. At the end of twelve and twenty-eight days, the alveoli in the solidified portions were filled with large numbers of greatly swollen mononuclear phagocytes, each of which contained a great many (from 15 to 40) small droplets of oil (fig. 11). The nuclei of these cells appeared small and shrunken, as though compressed by the closely packed oil droplets in the cytoplasm. At this stage, giant cells were not seen. An occasional oil-laden phagocyte could be seen in the walls of the alveolar duct, but on the whole, the framework of the lung appeared normal. Practically all of the oil present had apparently been taken up by the phagocytic cells.

In the cases of longer duration, while these oil-laden "foam cells" were still present, they were in smaller numbers, and an increasing amount of oil was present in the form of single large extracellular spherical masses with sharp borders. Around these masses of free oil, crescent-shaped giant cells were occasionally present, and in a few areas they were surrounded by concentric rings of newly formed connective tissue. A few of these large masses of free oil were still visible in paraffin sections, taking the eosin stain faintly. In focal areas, the alveolar walls in these cases showed a moderate widening and increased cellularity. The cells responsible for this appearance had oval vesicular nuclei and abundant cytoplasm, which often contained many oil vacuoles. These cells were consistent with young fibroblasts or "endothelial" cells in appearance, and seemed to be fixed cells, definitely a part of the alveolar walls rather than wandering cells. Mitotic figures were not infrequent among these cells, and it was difficult to escape the impression that they were the progenitors of the alveolar phagocytes. In spite of the volumes which have been written on it, this question is still unsettled.

Even in the case of longest duration (115 days), fibrosis of the alveolar walls was not found in a degree comparable to that observed in the two human cases in which mineral oil had entered the lungs.

The bronchial lymph nodes in these cases contained a large amount of oil (both free and within large mononuclear cells), and a similar appearance was observed in the solitary peribronchial and perivascular lymph follicles in the interior of the lung. Oil, however, was not found in the spleen or in other organs.

SUMMARY OF EXPERIMENTAL RESULTS

Vegetable Oils.—Disregarding chaulmoogra oil, which produces acute necrosis of the lung tissue, the three vegetable oils used in these experiments seem to be capable of remaining in the alveoli for months without producing any important reaction on the part of the fixed or wandering cells if infection is not present. In the case of the heavy iodized oils, minute abscesses were formed in two of fourteen animals, probably as a result of mechanical obstruction of the bronchioles.

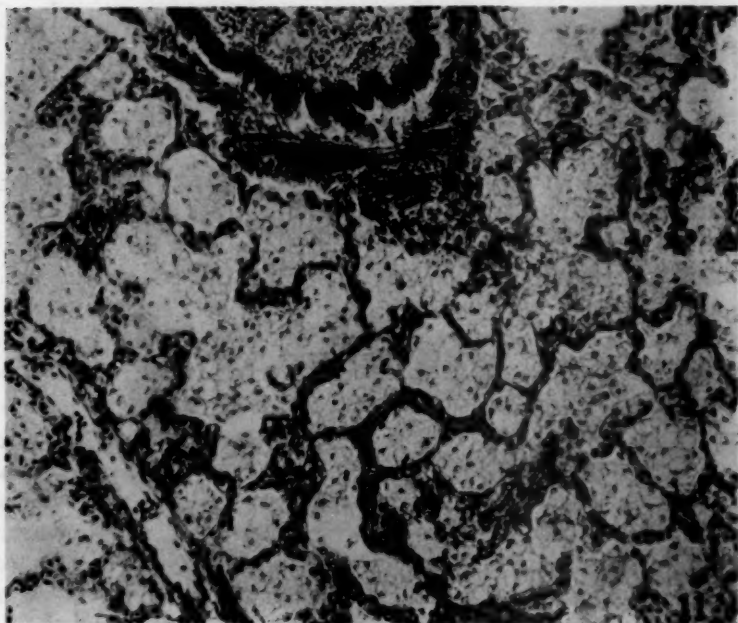


Fig. 11.—Mineral oil in the lung of a rabbit, stained by eosin-methylene blue, showing alveoli filled with vacuolated large mononuclears which contained finely emulsified oil. There is an increased cellularity of the alveolar walls.

Except for these occasional abscesses, which are probably infectious in origin, the lung tissue does not appear to be damaged in any way by the indefinitely continued presence of these oils in the alveoli. Microscopic evidence of hydrolysis or other chemical change in these oils does not appear after a prolonged stay (five and one-half months) in the lung.

Animal Oils.—The four animal oils employed produce marked consolidation of the lungs in a few days. This consolidation is found microscopically to be due partly to the presence of large mononuclear phagocytes, which fuse to form giant cells, but principally to connective

tissue proliferation. The degree of fibrosis and the rapidity with which it is produced vary considerably with the different oils. The masses of oil show irregularity and vagueness of outlines, suggesting that they are being decomposed. In the lung, certain chemical changes take place in these oils so that they become shreddy in appearance, insoluble in ordinary fat solvents and, in some cases, acid-fast. Rabbit fat is apparently incorporated and converted into adipose tissue, which is situated chiefly around the blood vessels and bronchioles. Lard oil produces rapid necrosis of the lung tissue, followed by repair, in which the epithelium of the lung participates in a remarkable manner, taking on an almost neoplastic activity.

Mineral Oil.—The reaction to mineral oil is distinguished by the very fine state of subdivision of the oil soon after its entrance into the lung, and by the rapidity and completeness with which the small globules are taken up by single large mononuclear phagocytes. The consolidation produced in a few days by the presence of this oil in the lungs is due entirely to the stuffing of the alveoli with these wandering cells. At the end of two or three months, formation of giant cells and fibrosis begin around large free masses of oil, apparently formed by coalescence of the small droplets set free by the phagocytic cells. After several months, a small portion of this oil becomes insoluble in fat solvents.

COMMENT

Intratracheal injection constitutes a unique method for studying the cellular reaction to foreign substances of varying degrees of solubility and irritability. When a foreign substance is injected intramuscularly or subcutaneously, the material is forced into the intercellular spaces; but under the conditions of these experiments, strictly speaking, it is not within the body. Its position is in many ways comparable to that of oil in the gastro-intestinal tract in that, at the beginning of the experiment, it is in contact only with cells of presumable epithelial origin.

The oil may gain entrance into the intercellular spaces in one of three ways: first, by passing directly through or between the alveolar epithelial cells in a fine state of subdivision (as is believed to be the case in the absorption of certain oils from the gastro-intestinal tract); second, by the intervention of wandering cells, which appear in the alveoli and ingest the oil, and third, by producing necrosis of the alveolar epithelium.

In two of the animals injected with iodized vegetable oil, in which infection coexisted, a rare bronchiole showed finely divided fat droplets in its epithelial cells, but there was not any good reason for believing that this fat represented the material introduced into the lungs. In

the case of cod liver oil, easily identifiable by its staining reactions, careful study seemed to exclude the possibility of absorption in this way. If this direct absorption occurs with the oils investigated, it must be on an extremely small scale.

In the case of animal and mineral oils, large mononuclears ingest the oil and carry it to the bronchial lymph nodes. The animal oils appear to be digested to a certain extent, and it seems probable that small amounts of these oils actually enter into the body metabolism. The conversion of rabbit fat in the rabbit's lung to what appears to be normal adipose tissue is of particular interest. It suggests that enzymes capable of "organizing" and storing a local excess of extra-cellular homologous fat are present in the lung. It is interesting to speculate as to why this storage takes place largely around the blood vessels and bronchioles. These are the only regions in the lung in which

Determination of Free Fatty Acid

	Cc. NaOH per Gram of Oil		Average	Acid Value
	Absolute Alcohol*	Acetone*		
Olive oil.....	0.9	0.8	0.85	2.4
Iodized poppy oil.....	0.6	0.7	0.65	1.8
Iodized sesame oil.....	0.9	0.9	0.9	2.5
Cod liver oil.....	0.7	0.5	0.6	1.7
Lard oil.....	6.4	6.6	6.5	18.0
Chaulmoogra oil.....	9.7	10.1	9.9	28.0
Mineral oil.....	0	0	0	0

* Ten grams of oil dissolved in neutralized solvent; titrated with sodium hydroxide, using phenolphthalein as indicator.

mesenchymal tissue is present in considerable amounts. On the other hand, the regions of storage correspond to the situation of the lymphatic vessels of the lung.

Mineral oil is apparently nearly inert, and is carried to the bronchial lymph nodes as a foreign insoluble substance. Its early ingestion by the large mononuclears may be due partly to the fact that it is quickly emulsified. Vegetable oils are not emulsified, and, as far as could be learned, leave the alveoli only by expectoration.

By reference to the table, it will be seen that the two oils which produce acute necrosis of the lung tissue are those which have by far the highest free fatty acid content. This suggests that the necrosis is caused by the free fatty acids. These acids are presumably sufficiently irritating to call into play the usual defensive mechanism (humoral and cellular). If this mechanism were inadequate, necrosis would result.

By assuming that the reaction to a fat or oil depends (1) on the amount of free fatty acid originally present and (2) on the rapidity with

which free fatty acid is formed (by hydrolysis) in the lung, it is possible to explain the experimental observations described satisfactorily.

In the case of the simple vegetable oils, practically no free fatty acid is originally present (table), and therefore there is no immediate reaction. It is more difficult to explain why these oils are not hydrolyzed by a prolonged stay in the lung. According to Lewkowitsch² and other observers, hydrolysis (at ordinary temperatures and at approximate neutrality) depends principally on two factors—moisture and enzymes, and the rapidity of the reaction depends partly on the concentration of these two factors. The moist alveolar gasses satisfy the first requirement, but the experimental observations seem to indicate that vegetable oils are practically unaffected by the lipases present in the lung.

It is a well known fact that lipases obtained from different organs vary considerably in chemical composition and in their action on different fats. Steapsin presumably works as rapidly on a vegetable oil as on an animal oil, but comparative data are not obtainable in the case of lipases from other organs. Gage and Fish,³ however, in studying the intestinal digestion of oils, found that castor oil, in spite of the fact that it contains palmitin (or stearin) in considerable quantities, is apparently not digested when given by mouth. (Purgative action did not occur until after the usual period required for the digestion of fatty substances.) The only other evidence confirmatory to the results obtained here is found in the work of Binet,⁴ who states that an animal oil (horse oil) injected subcutaneously is broken down and absorbed much more rapidly than a vegetable oil (olive oil). The confirmation of this apparent specificity of lung lipase for animal oils will be the subject of further study.

In 1920, Guieysse-Pellissier⁵ injected olive oil intratracheally and obtained an extensive large mononuclear response. His results appear to be contradictory to those recorded here, but they become explicable if one considers the fact that different samples of olive oil vary greatly in their free fatty acid content (from 0.3 to 25 per cent). It is probable that this worker used olive oil with a comparatively high content of free fatty acids.

2. Lewkowitsch, J.: *Chemical Technology and Analysis of Oils, Fats, and Waxes*, New York, The Macmillan Company, 1909.

3. Gage, H. G., and Fish, P. A.: *Fat Digestion, Absorption, and Assimilation*, *Am. J. Anat.* **34**:91 (Sept.) 1924.

4. Binet, L.: *Recherches physiologique sur la resorption de l'huile injectée sous la peau*, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:1458 (Nov. 20) 1925. Binet, L., and Fleury, P.: *Modifications chimique subies par l'huile injectée dans le tissu sous-cutané*, *Compt. rend. Soc. de biol.* **93**:1076 (Nov. 6) 1925.

5. Guieysse-Pellissier: *Recherches sur l'absorption de l'huile dans le poumon*, *Compt. rend. Soc. de biol.* **83**:809 (May 23) 1920.

The immediate necrosis produced by chaulmoogra oil is probably due to its high fatty acid content. The experiments do not give any evidence as to whether or not this oil is hydrolyzed further in the lung.

In the case of cod liver oil, the immediate effect is not injurious, because of the low initial acidity. This oil is rapidly hydrolyzed in the lung, however, and at first results in a reaction of large mononuclears and giant cells. Still later, the hydrolysis proceeds so rapidly that the fatty acids are formed faster than they can be neutralized, and the result is a slow necrosis in the lung tissue; this necrosis bears the same relation to the picture produced by lard oil that a chronic infectious process bears to an acute infectious process.

Mineral oil is a pure hydrocarbon, incapable of undergoing hydrolysis. It is apparently sufficiently irritating to evoke a tremendous cellular reaction, but does not produce chemical necrosis. The fibrosis which slowly follows the reaction to it is probably to be attributed to the natural tendency of connective tissue proliferation to follow the continued presence of large mononuclear phagocytes.

In the cases of cod liver oil and rabbit fat, the changes in the staining reactions observed suggest that the chemical changes undergone in the lung include something more than simply hydrolysis. The insolubility in fat solvents and acid-fastness which these oils acquire remind one of the physical properties of the semidrying and drying oils which form the bases of paints. It is probable that these oils undergo oxidation as well as hydrolysis. When "blown" or oxidized, an unsaturated fatty acid like oleic acid undergoes certain changes, among which are an increase in its specific gravity, a decrease in its iodine value and an increase in the so-called oxidized or hydroxylated fatty acids which are insoluble in petroleum ether. By passing air through cod liver oil, a thick gummy substance was obtained, which was nearly insoluble in ether and chloroform, and which, when stained with carbol fuchsin, was remarkably resistant to decolorization. The well known ability of potassium dichromate to render certain lipoids insoluble in fat solvents may also depend on oxidation.

The shreddy appearance assumed by the animal oils in the lung is probably caused by variations in surface tension as a result of the irregular mixing of the oil with the cytoplasm of the cell at the edges of the masses. If a drop of oil is placed in a mixture of glycerin and alcohol, it sends out pseudopod-like streamers, and assumes spider-like shapes quite similar to those exhibited by cod liver oil in the lung (fig. 5). By hydrolyzing the surface of the masses of oil, the enzymes make it somewhat soluble, so that the conditions are analogous to those existing in the simple experiment just described.

The lack of any such phenomenon in the case of a vegetable oil is what one would expect, in view of the immiscibility of neutral oil with such a fluid as cytoplasm.

Assuming that phagocytosis is essentially a surface tension phenomenon, it is possible to explain the accumulation of wandering cells and formation of giant cells about the masses of oil as a result of the outward diffusion of the soluble products of hydrolysis. One is at a loss, however, to explain in this way the reaction to a presumably insoluble and immiscible substance like mineral oil or carbon pigment, unless one assumes that the insolubility of such substances is only relative.

The fine state of subdivision of the mineral oil soon after its entry into the alveoli has been emphasized, and its behavior in this respect has been contrasted with that of the vegetable oils. The vegetable oils outside of the body are emulsified in water much more easily than the mineral oils. The reason for this extraordinary emulsification of mineral oil in the lung is not apparent, but may depend in some way on the activity of the phagocytic cells.

The question of the origin of the phagocytic cells involved in the reaction to these oils has not been dealt with, largely because such observations as have been made do not lead clearly and directly to any definite conclusion.

The epithelial changes obtained in the cases of lard oil and chaulmoogra oil are of such a nature as to suggest strongly that the presence of the oils played a large part in their production. This question is being studied further.

Most of the oils used in these experiments are crude products and are composed of mixtures of various lipoids, the chemistry of which is in many instances but poorly understood. In order to progress further toward an explanation of the phenomena reported, it would be necessary to work with single purified chemical substances.

These experiments were undertaken primarily to settle a point of practical importance, namely, the comparative merits of various oils for pneumography. Various substitutes for the simple vegetable oils have been proposed (including animal oils, such as lard oil), but, as far as can be learned, histologic studies to support these recommendations have not been made on the lung tissue. Animal oils seem to be definitely contraindicated, judging by the results obtained in these experiments.

It has been stated repeatedly that certain oils are best adapted for pneumography because they are rapidly absorbed. It would seem from the results set forth in this paper that the ideal oil for intratracheal injection is the most inert and least absorbable oil; or, if the foregoing deductions are correct, the oil which has the lowest acid value and is least susceptible to the action of lung lipase.

An interesting observation has been made by Simonds ⁶ on the lesions produced in the lungs by emboli composed of suprarenal tissue. The reaction to these particles of lipoid-containing tissue is similar in many ways to the reactions to the animal oils already described, especially cod liver oil. Simonds points out the resemblance of these lesions to those produced by the tubercle bacillus, which have been thought by some to depend largely on the presence of lipoids.

In 1899, Auclair ⁷ believed that he was able to produce the histologic picture of tuberculosis by injecting the ether extract of dead tubercle bacilli into the lungs of animals. As far as can be learned from his description and illustrations, he produced areas of necrosis in the lung comparable to those produced in these experiments by cod liver oil and lard oil, and it seems probable that the necrosis which he obtained was caused by the fatty acids originating from the bacterial fat.

The resemblance of lesions produced by the reaction to necrotic fat (chronic mastitis, cholecystitis, prostatitis, etc.) to those produced by the tubercle bacillus does not need comment. The chemical changes which "dead" or extracellular fats and oils undergo in various tissues and the lesions produced under pathologic conditions by their decomposition products are worthy of further study.

CONCLUSIONS

1. Animal, mineral and vegetable oils, injected intratracheally, disappear slowly from the lung, requiring a period of several months for complete removal.

2. In the absence of infection, the simple neutral vegetable oils (iodized sesame and poppy seed oil and olive oil) practically do not produce any reaction, and did not appear to injure the lungs in any way. Their removal from the lungs appears to be accomplished entirely by expectoration.

3. Animal oils (milk fat, rabbit fat, cod liver oil and lard oil) caused marked fibrosis and giant cell formation in the lungs in a few days.

4. Mineral oil is quickly emulsified and taken up by phagocytic cells in the alveoli, and consolidation of the lung is produced. Giant cell formation and slight fibrosis are evident at the end of the second or third month.

5. Free fatty acids derived from certain animal oils produce caseation necrosis in the lung tissue. The degree of damage and result-

6. Simonds, J. P.: The Organization of Experimental Adrenal Cell Emboli in the Lungs, *Am. J. Path.* **3**:13, 1927.

7. Auclair, J.: Les poisons du bacille tuberculeux humain, *Arch. de méd. expér. et d'anat. path.* **11**:363, 1899.

ing fibrosis produced by an oil in the lung depends largely on the amount of free fatty acid originally present and on the rapidity with which hydrolysis progresses.

6. The almost complete lack of reaction to the neutral vegetable oils in the lung is probably due to the absence of enzymes capable of hydrolyzing the oil.

7. The simple neutral vegetable oils (such as poppy seed and sesame oil) appear to be most suitable for introduction into the lungs for roentgenologic purposes.

8. Animal and mineral oils, injected intratracheally, are deposited in the bronchial lymph nodes; vegetable oils are not.

9. Cod liver oil and rabbit fat undergo a change in the lungs and became acid-fast. They also become insoluble in the ordinary fat solvents. This, as well as the similar action of potassium dichromate on certain fats, is probably due to oxidation.

10. Rabbit fat alone of the injected substances is "organized" and stored locally in the form of wide zones of fatty tissue especially about the blood vessels.

11. Epithelium may participate in the repair of a suddenly produced area of necrosis in the lung, and, in so doing, may take on an almost neoplastic activity.

EMBRYONAL CARCINOMA OF THE OVARY *

ELISE S. L'ESPERANCE, M.D.

NEW YORK

The solid carcinomas of the ovary form a large and somewhat heterogenous group of neoplasms with widely differing histologic structure and an equally diverse histogenesis. Among this varied group there is an uncommon, though interesting, type which usually occurs in young subjects, pursues a rapid course, often associated with early wide metastases, and frequently is fatal. The histologic structure, which exhibits distinctly embryonal characters, is composed of small rounded or polygonal cells with large hyperchromatic nuclei growing diffusely in a typical lymphoid stroma. For this undifferentiated type, the term "embryonal" or "teratoid" carcinoma is employed. Although this term has long been accepted to designate certain characteristic tumors of the testis, it is not, so far as I have been able to find, generally accepted in the literature to identify similar conditions in the ovary.

In presenting the following cases, I wish to emphasize the resemblance in histologic structure, gross anatomy and clinical course which exists between this indefinitely classified group of tumors of the ovary and the teratoid embryonal carcinomas of the testis, and to demonstrate a similar histogenesis and therefore a teratoid origin for many of the solid carcinomas of the ovary in young persons.

REPORT OF CASES

CASE 1.—History.—A married woman, aged 19, entered the New York Infirmary with the complaint that for five months she had noticed a rapid increase in the size of the abdomen. There was little of note in her past history, with the exception of a late onset of menstruation and extreme irregularity during the two years following. Her development was imperfect, as shown by the absence of pubic and axillary hair and small external genitals and breasts. The abdominal enlargement was symmetrical and about the size of a six months' gestation. At operation, bilateral tumors were found involving both ovaries.

Gross Structure.—The right ovarian mass was distinctly lobulated, fairly well encapsulated with slightly roughened surface, and measured 20 by 14 by 7 cm. Across the long diameter of the tumor, there was a thickened uninvolved fallopian tube with attached broad ligament. The bulk of the tumor was composed of creamy white, homogeneous soft material. Firm silvery strands radiated from a central portion and divided the mass into sectors. The left ovarian mass was much smaller, slightly lobulated and encapsulated and retained the outline of the ovary. A thickened fallopian tube was attached to the surface.

Microscopic Examination.—The tumor consisted of diffusely arranged, rounded or polyhedral cells, with indefinite granular cytoplasm and indistinct cell borders. The nuclei were large, usually single and hyperchromatic. In certain

* From the Department of Pathology, Cornell University Medical College.

areas, the cells of the tumor were limited to groups or nests separated by a delicate spindle-cell stroma and thickly infiltrated with lymphocytes and plasma cells (fig. 2). This lymphoid stroma was present in varying amounts in all sections of the tissue. Occasional large cells with multilobed nuclei and others in different stages of atypical mitosis were seen. The blood vessels were numerous

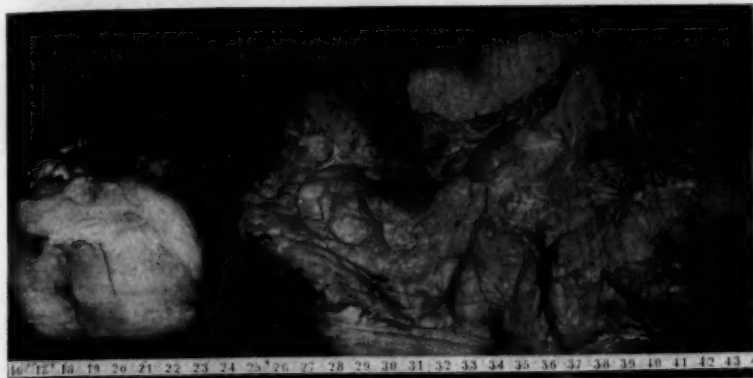


Fig. 1 (case 1).—Gross appearance of bilateral embryonal carcinoma of ovary. The variation in the size and the nodular surface should be noted.

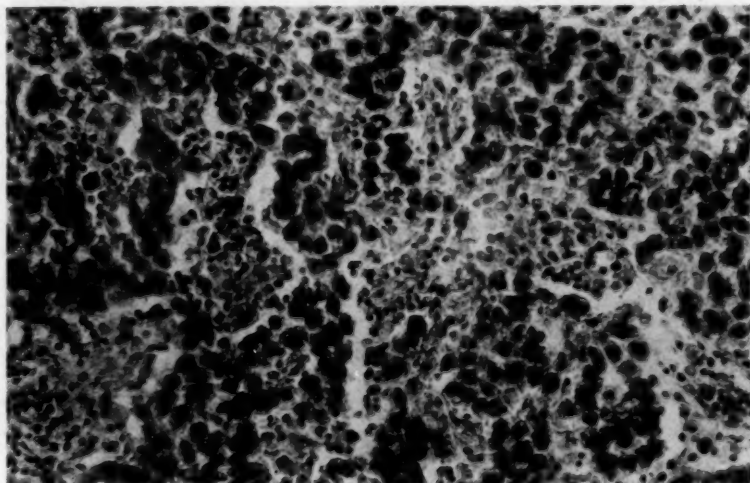


Fig. 2 (case 1).—Histologic picture of embryonal carcinoma with lymphoid stroma.

and varied in size from those with definite walls to small capillaries. Around the larger vessels, the cells of the tumor appeared to invade the wall, leaving the flattened endothelial lining intact and giving a peritheliomatous structure. Many of the small spaces, which suggested lymph spaces, were filled with emboli of tumor cells. In one area, an unruptured graafian follicle was found with membrana granulosa and definite swollen theca cells surrounding it. The tumor cells

completely encircled this structure, which appeared undisturbed by its dangerous neighbors.

The smaller ovarian mass revealed a histologic structure almost identical with that of the larger one, with the exception that it was less vascular. The lymphoid stroma was more prominent, and the cells assumed a diffuse arrangement.

CASE 2.—History.—A girl, aged 17, who had never menstruated, complained of gradual increase in the size of the abdomen. At operation, the tumors were bilateral, encapsulated and of unequal size.

Microscopic Examination.—The structure was that of a characteristic embryonal carcinoma with lymphoid stroma. The only variations in the histologic picture

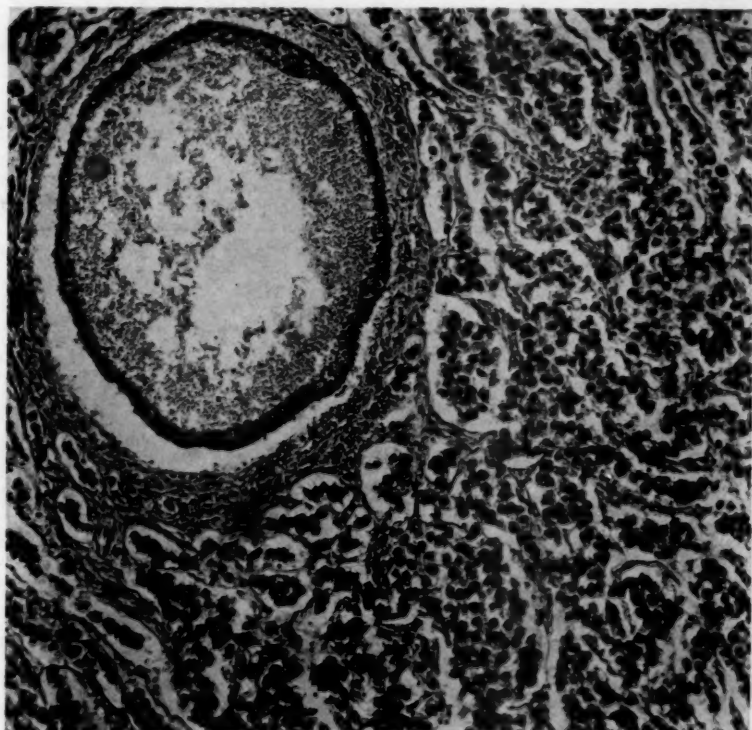


Fig. 3 (case 2).—Embryonal carcinoma. Arrangement of cells in strands separated by fine hyaline tissue with many lymphocytes. The maturing graafian follicle with the theca infiltrated with cancer cells should be noted.

were the occasional arrangement of the cells in single strands, which were separated by fine fibrillar hyaline tissue and many islands of lymphocytes (fig. 3).

Comment.—The histologic features of these two cases so exactly coincide with Ewing's description of the typical embryonal carcinoma of the testis that it seems reasonable, on this evidence alone, to assume a similar and therefore a teratoid origin for carcinoma of the ovary with lymphoid stroma. The distinct encapsulation was undoubtedly a factor in the favorable outcome. Both patients survived without recurrence for two years.

CASE 3.—History.—A married woman, aged 23, who had never been pregnant, for a short time had noticed a rapid enlargement of the abdomen. At operation, a semisolid encapsulated ovarian tumor was found, about the size of a six months' gestation. The central portion was necrotic, with a thick ragged wall.

Microscopic Examination.—The cells exhibited a perithelial arrangement, but their form and structure were identical with those of the cells encountered in the first two cases, and the stroma was composed of lymphocytes.

Comment.—Necrosis was a prominent feature in this case. The growth was rapid, and the tumor vascular. The extreme vascularity, with resulting hemorrhage, was undoubtedly an important factor in the extensive necrosis, and the combination had much to do with the perithelial architecture of the main tumor. Nevertheless, on the basis of the morphologic structure of the cells and the lymphoid stroma, it is justifiable to include it in the series as an embryonal carcinoma.

Cases 2 and 3 were submitted by Dr. Caturanni for diagnosis.

CASE 4.—History.—A girl, aged 16, with recurrent carcinoma of the ovary, entered Dr. Healy's service at the Memorial Hospital. Five months previously, she was operated on for acute appendicitis, and at that time a round cell sarcoma was diagnosed. This recurred in three months, and a second operation was performed. Three months later, there were recurrences in the abdominal incision and, even with vigorous radiation therapy, the patient survived only a few months.

Gross Examination.—A large cyst filled with branlike material and hemorrhage, with several firm nodules on the inner surface, was found. There were evidences of peritoneal adhesions and invasion of the capsule by carcinoma.

Microscopic Examination.—The tumor was composed of areas of aveolar carcinoma, with rows and nests of large polyhedral cells and occasional acidophil cells resembling muscle cells. The nuclei were faintly stained, giving the impression of early necrosis. The stroma was a delicate network supporting myriads of lymphocytes and few plasma cells (fig. 4).

Comment.—The tumor was unilateral and was mistaken clinically for appendicitis. The course was extremely rapid with early local recurrence and apparently a distinct morphologic change in cell characters. The earlier structure was a round cell "sarcoma." In the local recurrence, the cells had become polyhedral, giving the picture of an alveolar carcinoma, but the lymphoid stroma with islands of lymphocytes was characteristic of embryonal carcinoma of the sex glands.

CASE 5.—History.—A girl, aged 15, seen at Bellevue Hospital, with increasing distention of the abdomen, presented little of interest in her history, except that she had never menstruated. At operation, the right ovary was found converted into a solid, partially encapsulated mass which was adherent to the uterus. Its outer surface was covered by many rounded protuberances, some of them hemorrhagic. The substance was spongy, friable, grayish material.

Microscopic Examination.—The left ovary was not involved. The right one was transformed into a mass of embryonal cells in columns and cords, sometimes in nests or alveoli. Between these cells there was a delicate network of fibrils, many lymphocytes and extensive necrosis and hemorrhage.

Comment.—This case was similar to case 4. In both, the carcinomas were unilateral and not encapsulated and had involved the peritoneal surface at the time of operation. Necrosis and hemorrhage formed a striking feature in each

case and obscured any original structure. There was early recurrence with variation in cell type, extensive metastases and fatal termination within a year.

CASE 6.—History.—A woman, aged 46, was referred by Dr. Felsen for diagnosis. She had never menstruated and had been married seventeen years and had not been pregnant. For the past five months she had complained of severe pain in the lower part of the abdomen, with some distention. Palpation revealed a small tumor mass on the right side, and by vaginal examination, the cervix could not be found. At operation no trace of the tubes, ovaries or uterus could be found in the pelvis. On the left side, in what appeared to be the broad ligament, a small firm mass was found about the size of an atrophic ovary. On the right side, at the brim of the pelvis, there was a well encapsulated firm tumor about the size of a grapefruit. This was loosely retained in position by a fold of peritoneum.

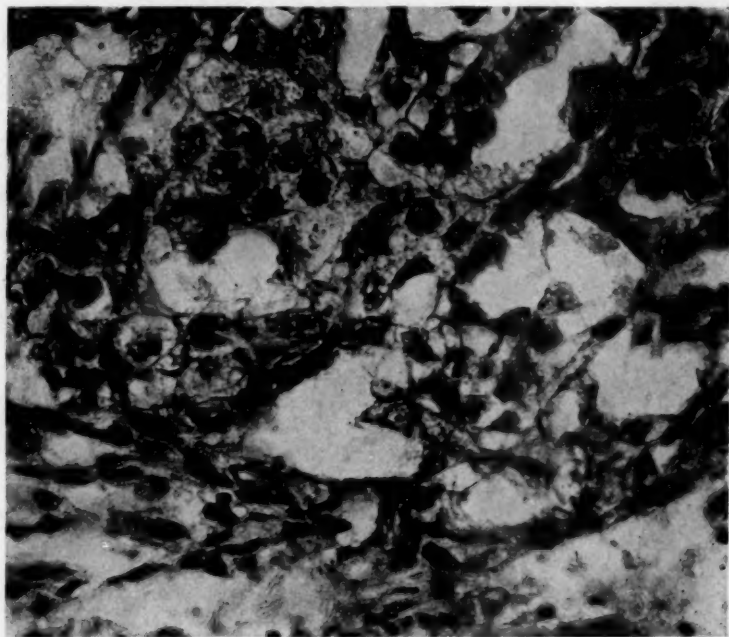


Fig. 4 (case 4).—Recurrent embryonal carcinoma of ovary. Large polyhedral cells lymphoid stroma.

Gross Anatomic Examination.—The tumor was enclosed in a firm capsule with a smooth surface. On cross-section the bulk of the mass, which was white, was composed of rather soft homogenous material surrounding an eccentrically placed circumscribed darker area, which appeared firm and glistening, almost like cartilage.

Microscopic Examination.—The main portion of the tissue consisted of a diffuse growth of rounded undifferentiated cells in a delicate lymphoid stroma, characteristic of embryonal carcinoma. The smaller area was composed, for the most part, of dense hyaline tissue with isolated islands of embryonal cells of the same type as the larger mass. Many parts were necrotic. A peculiar feature was the presence of a smooth noncellular material which resembled cartilage.

Comment.—This case was of particular interest in that it revealed two distinct types of the tumor tissue, one composed of a diffuse growth of embryonal cells and the other consisting of dense hyaline-like material. The bulk of the embryonal tissue, as compared with the smaller portion of the tumor, showed the rapidity with which a single malignant element in a teratoma can replace all other structures and appear as a carcinoma. Furthermore, the location of the mass at the brim of the pelvis suggested a close analogy to the embryonal carcinoma developing in undescended testes. Another unique feature was the complete absence of derivatives of the mullerian anlage, uterus and tubes, indicating an early embryonal disturbance. The fact that the normal functions of the sex organs were completely inhibited may account, in part, for the long period of quiescence. This patient was the only one in the series who was more than 23 years of age.

In the interpretation of these cases, several points may be emphasized as corroborative evidence of their embryonal origin. The age incidence, usually before the twentieth year, and the rapid development at, or near, puberty imply an interrelation between functional activity and their excessive capacity for growth. That the same stimulation which incites the onset of normal function, when applied to isolated, imperfectly developed sex cells, may activate the enormous capacity for growth, latent in these cells and may result in the production of this highly malignant neoplasm, seems reasonable and supports their embryonal nature.

In all of the cases in this series, the carcinomas were associated with disturbances in ovarian function manifested by late onset or complete absence of menstruation, irregularity, sterility and more or less imperfect development of sexual characteristics. In one case, there was a complete absence of the uterus and tubes and an arrested development of both ovaries. The significance of these facts is not altogether clear. However, it is further evidence of their congenital origin.

GROSS ANATOMY

In two of the cases, the carcinomas were bilateral and well encapsulated. This encapsulation was apparently an important factor in their favorable course. Four of the carcinomas were unilateral. One had undergone extensive necrosis and this accident, by limiting the growth and preventing metastases, may account for the favorable outcome. Two of them were highly malignant, with extensive local recurrence and wide distribution, and proved fatal within a year. In neither of these cases was the tumor encapsulated. In fact, at the time of operation there was involvement of the peritoneal surface in both. In the other case, the tumor occupied an eccentric position at the brim of the pelvis and was firmly encapsulated. There was little evidence of formation of cysts in any of them, except secondary to necrosis. In this respect, they differed from solid carcinomas of adult type in which cysts form a prominent feature.

MICROSCOPIC VARIATIONS

The histologic structure varied from small round cells with little cytoplasm to larger ones with acidophil cytoplasm. The architecture usually maintained a diffuse growth with some tendency to produce epithelial nests and occasional perithelial rosets. Sometimes the structure of an alveolar carcinoma was prominent in various areas of the tumor. The characteristic lymphoid stroma was present in all the cases and replaced the typical supporting tissue of the adult type of solid carcinoma. This feature appears characteristically in the embryonal carcinomas of the sex glands. I do not know of its frequent occurrence in other epithelial tumors.

THEORIES OF ORIGIN

The various theories which have been advanced to explain the origin of teratoma testis may be applied to this group of neoplasms. The soundest theory is that the neoplasms arise from sex cells, the normal development of which has been suppressed but the potencies of which remain intact, ready to express themselves in the various forms of simple or complex teratoma (Ewing¹). In the ovary, the condition is somewhat more complex than in the testis. The sex glands are widely separated from one another, and bilateral tumors are frequently encountered. These may arise as a spontaneous development in both ovaries, or by metastases from one focus. The theory of a spontaneous origin is considered on the ground that, as these tumors probably arise from undifferentiated sex cells, the condition for their development may exist in both ovaries, and the factors which determine one growth may produce the other, either at the same time or at a later stage. Cystic teratomas, the common dermoids, for example, may and frequently do arise in both ovaries, nearly always during the early functional activity of these glands. On the other hand, the wide variation in size in the bilateral tumors might favor a metastatic origin. In the bilateral cases reported, evidence of extension in the broad ligament or permeation through the lymphatics was not present, nor were distant metastases found, which certainly does not favor a metastatic origin. Two of the carcinomas which were unilateral and highly malignant did not present either a histologic or a gross indication, of involvement of the opposite ovary, which is corroborative evidence for a spontaneous origin in the bilateral type.

HISTOGENESIS

The uncertainty regarding the histogenesis of these tumors seems to have led to much confusion in the literature. Many appear as

1. Ewing: *Neoplastic Diseases*, 1922; *Surg. Gynec. Obst.* **12**:230, 1911.

endotheliomas. Bernstein's² case of endothelioma of the ovary in a child, aged 11 years, gave the histologic picture of embryonal carcinoma with typical lymphoid stroma. Endothelioma of the ovary is a disputed subject. Aschoff³ disposed of it in the brief statement, "all such tumors are carcinoma," and this view was confirmed by the observations of Ribbert,⁴ Meyers,⁵ Ewing¹ and others. Coe and Coley⁶ described a perithelial sarcoma in a young subject with the microscopic picture of rounded undifferentiated cells with perivascular arrangement in a lymphoid stroma. A round cell sarcoma in a girl, aged 15, described by Porter,⁷ gave the typical diffuse growth of round cells in a lymphoid stroma. Donhauser reported an adenosarcoma in a child, aged 13 years, which he considered as probably embryonal. He reviewed seventy-two cases of malignant ovarian tumors in children aged from 22 months to 15 years. Carcinoma of the ovary in a child, aged 11 years, was described in great detail by Lahey and Haythorne.⁸ This tumor pursued a rapid course with extensive metastases and histologically revealed typical characters of embryonal carcinoma. Knott⁹ reported a case of carcinoma of the ovary in a child, aged 11 years, in which he found hyaline cartilage, stratified cells and muscle bundles in a mass of diffusely growing polyhedral cells with lymphoid stroma. The development of a single element in a teratoma is amply verified in the literature. A single element may predominate and obscure, or even suppress, all other structures (Pick). This is demonstrated in the overgrowth of thyroid in struma ovarii. In one of Ewing's cases of embryonal carcinoma of the testis, he was able to find only a small island of cartilage and a single epidermoid cyst to support the tridermal origin. The neoplasm was small and the deduction was drawn that if it had remained unmolested, the capacity of the carcinoma for growth would soon have outstripped these smaller elements, resulting in a diffuse growth of embryonal cells without evidence of its teratomatous nature. It seems reasonable to apply a like hypothesis to the atypical ovarian tumors.

On account of the anatomic position of the ovaries, an early diagnosis is seldom made until a single element so far exceeds any remaining structure of slower growth, that it appears as a diffuse carcino-

2. Bernstein: New York M. J. **85**:110, 1907.

3. Aschoff: M. G. G. **9**:38, 1899.

4. Ribbert: Die Lehre von die Geschwulsten, Bonn, 1904.

5. Meyers: Arch. f. Gynäk. **109**:212, 1918.

6. Coe and Coley: M. Record **71**:436, 1907.

7. Porter: J. Indiana M. A. **8**:119, 1915.

8. Lahey and Haythorne: Am. J. M. Sc. **143**:257, 1912.

9. Knott, Van Buren: Ovarian Carcinoma in a Child, Aged Eleven, J. A. M. A. **64**:1577 (May 8) 1915.

matous process, replacing not only any tridermal remnants but the normal structures of the ovary as well.

TREATMENT

The best method of treatment in these neoplasms is still a disputed question. Operative procedure resulted in cures for three years in three of the cases. An important factor in producing these favorable results was undoubtedly due to the complete encapsulation of the tumor. The two patients in whom the outcome was fatal were subjected to extensive operations with an unfavorable result. Radium was used in only one of the cases reported, and then only after the third recurrence. Failures with treatment by radium are frequent in recurrent tumors, which explains the unsatisfactory result in this case. Radiation therapy is extremely successful in treatment of tumors of embryonal cells. The more undifferentiated the cell characters, the more readily they react to radiation. Considerable success has been obtained in the treatment of the embryonal carcinomas of the testis by radiation, and it is logical to expect the same results in similar tumors of the ovary.

The most conservative treatment, with the present knowledge, is operation and postoperative radiation.

CONCLUSIONS

While difficulties surrounding the morphologic interpretation of any neoplasm are obvious and as conditions in the ovary are far more complex than in the testis, nevertheless the striking similarity between this group of tumors and the embryonal teratoid carcinomas of the testis seems to justify maintaining, on the basis of analogy, an identical histogenesis, and therefore a teratomatous origin, for the embryonal carcinomas of the ovary.

A review of the literature demonstrates the uncertainty regarding the histogenesis of many of the malignant ovarian neoplasms in young persons. These morphologic variations were paralleled in some of the histologic pictures encountered in the cases reported and appear to warrant the assumption that many, if not all, of the atypical malignant tumors of the ovary that occur in young subjects have a teratoid origin.

EFFECT OF PILOCARPINE AND EPINEPHRINE IN THE PRODUCTION OF SPECIFIC LESIONS IN THE STOMACH OF RABBITS *

FRANK P. UNDERHILL

AND

JOHN M. FREIHEIT

NEW HAVEN, CONN.

The etiology of chronic ulcer of the stomach and the duodenum has long been a subject of discussion. Anatomic, physiologic and clinicopathologic studies have fostered the elaboration of many theories relative to the production of such lesions, but experimental confirmation of one or any of these has never been accomplished satisfactorily.

The concensus of opinion is that chronic ulcer in man develops from an acute ulcer which in turn is preceded by an initial lesion. This initial lesion has been attributed to a variety of causes which bring about chiefly a circulatory disturbance in a limited area of the gastric or duodenal mucosa. Once the initial lesion is induced, secondary factors, such as irritation by food, posture, acidity, infection or antibody destruction, bring about the acute lesion which sometimes becomes chronic. The importance of the gastric juice and acid in the causation of ulcer is believed to have been overestimated, and it is now held that gastric juice can produce lesions only when the tissue which it destroys is already pathologic. The same is true of infection, for the general argument seems to favor infection as secondary to a pathologic lesion.

The number of possible etiologic factors which bring about the cause of circulatory disturbance in the stomach is so great, and in many cases the combination of factors is so complex that it seems improbable that one should expect to find a single cause of gastric or duodenal ulcer.

A few of the commonly stated theories concerning the production of ulcer may be summarized briefly as follows: (a) Virchow regarded embolism or actual disease of the afferent vessels as responsible for gastric ulcers. (b) Irritation due to hydrochloric acid and other substances within the stomach has been suggested in explanation of the production of ulcer. (c) External trauma, often of occupational origin has been mentioned. (d) Gastric ulcer has been attributed to the effect of micro-organisms. Chronic and acute lesions have been reported from a large number of organisms. (e) Heredity has been held responsible for the production of ulcers. (f) Asthenic constitution and nervous origin remains a prominent theory. (g) Parasites in the stomach have been suggested as a cause.

* From the Department of Pharmacology and Toxicology, Yale University.

Of all the theories proposed, the one that has received most indorsement at present is that of the nervous origin of ulcer. Experiments conducted recently attempt to imitate constitutional anomalies found in man. Reliable statistical data by von Cackovic¹ and Westphal and Katsch² show that neuroses precede ulcers. According to Eppinger and Hess,³ various degrees of tone of the stomach present themselves in different persons, varying with the predominance of vagus or sympathetic innervation of the stomach and the intestines. The presence or absence of excess tonus is determined by the injection of minute amounts of pilocarpine or epinephrine, the patient who is hypersusceptible to pilocarpine presenting enumerated symptoms indicative of vagus tone or vagotonia. Similarly, the patient who is hypersusceptible to epinephrine presents symptoms that are indicative of increased sympathetic tone or sympatheticonia. The symptoms of hypersusceptibility to these drugs, however, so frequently overlap that it is preferable to refer to them as being due to vegetative stigmas rather than to vagotonia or sympatheticonia.

Vegetative stigmas are found in the majority of patients with chronic gastric and duodenal ulcers. Westphal and Katsch have enumerated the stigmas in patients with gastric ulcers, finding that the majority of these patients were susceptible to pilocarpine while others responded to a combination of pilocarpine and epinephrine. From an analysis of 172 cases of operatively demonstrated ulcer, von Cackovic has concluded that vegetative stigmas are usually found in young persons, and so the initial lesion of peptic ulcer may have an early origin and arise from the same underlying factors. According to this view, ulcer may be looked on as the end-result of a constitutional disturbance.

Basing their experiments on these clinical observations and assuming that vegetative stigmas precede the development of ulcer, Westphal,⁴ in Germany in 1914, and Friedman,⁵ in the United States in 1918, attempted to produce conditions in rabbits somewhat simulating vegetative stigmas found in man, by injection of pilocarpine, a drug whose action in the parasympathetic nerve-endings produces the following objective symptoms: (1) increased secretions: (a) profuse salivation, (b) lacrimation, (c) bronchial râles; (2) increased intestinal tonus—diarrhea, and (3) contraction of the pupils.

Westphal injected subcutaneously from 2.5 to 5 cg. doses of pilocarpine, varying from 10 to 30 cg. per kilogram of body weight within time limits varying from two hours to several days, and found on

1. Von Cackovic, L.: *Arch. f. klin. Chir.* **98**:570, 1912.

2. Westphal, K., and Katsch, G.: *Mitt. d. Med. u. Chir.* **26**:391, 1913.

3. Eppinger, H., and Hess, L.: *Ztschr. f. klin. Med.* **67**:345, 1909; **68**:205, 1909.

4. Westphal, K.: *Deutsches Arch. f. klin. Med.* **114**:327, 1914.

5. Friedman, G. A.: *J. M. Research* **38**:449, 1918.

killing the animals that rather consistently lesions of the gastric mucosa were produced which they record as "erosions" or "acute ulcers," depending on the gross appearance. With this technic, occasional lesions of the first portion of the duodenum are also reported. Friedman injected alternately at twenty minute intervals pilocarpine in 2.5 cg. doses in total amounts up to 0.5 to 0.75 cg. per kilogram, and a stock solution of epinephrine in 0.1 cc. doses up to total quantities of 0.15 to 0.20 cc. per kilogram for a period of two hours. He claimed that the lesions produced in the majority of cases were duodenal and pyloric. Epinephrine injected alone did not cause lesions in rabbits.

The theory that both investigators advance for the formation of the lesions, and which Westphal elaborately endeavors to prove, is that pilocarpine, by its action on the parasympathetic nerve-endings in smooth muscle, causes localized areas of spasm in the smooth muscle which occlude small arterioles passing through these areas, the diminished circulation thus produced causing a necrosis of the overlying mucosa supplied by the constricted vessels. This necrotic mucosa is sloughed away by the combined action of food and acidity, leaving an ulceration. Friedman asserted, in addition, that the combined effects of pilocarpine and epinephrine produce a simultaneous hypertonicity of both vagus and sympathetic nerves, a condition not infrequent in man, especially manifested clinically in exophthalmic goiter in which symptoms of vomiting, diarrhea and perspiration indicate vagotonia and tachycardia, and glycosuria and exophthalmos indicate sympatheticotonia; this picture is often associated with ulcer of the stomach or duodenum. The mechanism of production of the lesion is supposed to be similar to that caused by pilocarpine alone.

Westphal carried through similar experiments with pilocarpine and a combination of pilocarpine and epinephrine with cats, dogs and guinea-pigs. In four of nine cats he demonstrated "erosions" at autopsy, but he does not state whether these occurred when pilocarpine alone was used or when the drugs were combined. He produced two small "ulcerations" in the pyloric area in two of four dogs; the other two yielded negative results. In three guinea-pigs, small miliary hemorrhages were produced in the mucosa, apparently not associated with loss of substance. Microscopic observations are not reported. It is admitted that much less satisfactory results are produced with these animals than with rabbits, and the differences are attributed in rabbits to the diminished capacity of the mucosa to withstand the action of the gastric juice on the initial lesion. This argument is associated with that in a report of Kawamura in which he said that lesions of the celiac ganglion increase the disposition to the formation of ulcer, which, similarly, is attributed to diminished resistance of the mucosa of the rabbit. In dogs, under

similar circumstances, it is not marked. Westphal concluded that this peculiarity renders the rabbit a desirable animal for this type of study.

It is to be noted that all the lesions produced by the foregoing investigators were acute. All attempts to produce chronic ulceration failed. Although the investigations with pilocarpine have given results only in terms of acute lesions, they derive their chief merit from the alleged specificity of the mechanism of production. The explanation for the failure of ulcerations produced by pilocarpine to become chronic is attributed to the fact that an actual constitutional disturbance is not produced by the technic employed. By producing constitutional disorder through partial extirpation of thyroids and parathyroids, Friedman claimed a marked tendency of such lesions against healing. Finze noticed the delayed tendency of acute lesions to heal after partial supra-renalectomy.

The present investigation was planned in order to study more closely the interesting results of Westphal and Friedman and, in particular, the alleged specificity of pilocarpine and epinephrine.

EXPERIMENTAL PRODUCTION OF LESIONS BY PILOCARPINE AND BY PILOCARPINE AND EPINEPHRINE

Methods.—Pilocarpine was injected subcutaneously into rabbits in varying dosages. On the day previous to the administration of the pilocarpine, the animals had received diets of cabbage, cabbage and oats, oats and turnips or of oats alone. Food was not given on the day of the experiment; water was always available. A few animals were fasted for two or three days previously. At the end of the experiment, most of the animals were killed by stunning and bleeding; a few died spontaneously. In some rabbits injections of pilocarpine were alternated with intravenous injection of 0.1 cc. doses of epinephrine solution 1:1,000.

TYPICAL EXPERIMENTS WITH PILOCARPINE ONLY

Only illustrative examples of the experiments will be outlined. These experiments merely represent a member of each type and have been amply confirmed.

EXPERIMENT 1.—A male rabbit, weighing 2.1 Kg. that had been fed on a diet of cabbage and oats the previous day, received 0.5 cc. of 5 per cent pilocarpine solution subcutaneously at 2:40 p. m. Within five minutes, salivation and loose stools were in evidence. At 2:50 p. m., 1 cc. of the pilocarpine solution was injected. Salivation became profuse, the respiration increased and the animal became very restless. A third injection of 1 cc. of pilocarpine solution was given at 3:10 p. m. Bronchial râles could be heard now without the aid of a stethoscope. A fourth injection of 1 cc. of pilocarpine solution was given at 3:36 p. m., a fifth at 3:40 and a sixth at 4:10. The rabbit was now in considerable respiratory distress; salivation was still profuse, and soft stools were passed; respiration was very slow. In all 27.5 cc. of pilocarpine was injected. The rabbit was killed at 4:30 p. m. Immediate autopsy revealed the stomach contracted and undergoing slow peristalsis; the small intestine, empty and

vigorously contracting. When the stomach was opened along the lesser curvature two lesions were noted, one on either side of the line of the greater curvature just esophageal to the contraction band; the larger measured 7 by 4 mm., and the other 5 by 4 mm. The lesions were oval and possessed a slight depth, the base being represented by a brown hemorrhagic area about two thirds the size of the lesion. Within from 1 to 2 cm. of these lesions, still on the cardia, were three hemorrhagic areas the size of a pinhead, seemingly without loss of substance. Lesions were not found in the small intestine, cecum, appendix or colon.

Microscopic section of the larger gastric lesion revealed a punched-out erosion of the superficial portion of the mucosa, which did not extend through to the submucosa. There was no evidence of exudation or hyperemia of the submucosa or adjacent mucosa.

EXPERIMENT 2.—A male rabbit, weighing 1.95 Kg., had been fed on cabbage. One injection of 0.5 cc. of 5 per cent pilocarpine solution was given at 2 p. m. Salivation and loose stools resulted. The rabbit was killed at 4 p. m. The stomach and intestines did not contain any lesions.

EXPERIMENT 7.—A male rabbit, weighing 1.6 Kg., that had been fed previously on a diet of cabbage received injections of pilocarpine solution (5 per cent) as follows: 10:40 a. m., 0.5 cc.; 10:55, 1 cc., and 11:10, 1 cc. Salivation, loose stools and respiratory distress were in evidence. The animal died at 1:30 p. m. Immediate autopsy showed that the abdominal cavity contained 100 cc. of brown fluid and intestinal contents. The stomach was markedly contracted, the duodenum empty and black, and perforated about 2 cm. from the pylorus. When the stomach was opened, two large irregular lesions and thirteen small oval lesions were found around the contraction ring, varying from 1 to 5 cm. in the largest diameter. Higher in the cardia were numerous lesions the size of a pinhead that had characteristically smooth edges, sloping sides and a hemorrhagic smooth base, without induration or undermining. In the pyloric mucosa were three ulcers; the largest was oval, quite deep, and measured 5 by 3 mm.; the other two were smaller. The duodenum was almost black and very friable, breaking off on removal at the point of perforation. This condition of the duodenum did not extend beyond 10 cm. from the pylorus. The remainder of the intestines was free from lesions.

Microscopic section of the largest lesion showed an erosion of the mucosa, not extending to the submucosa, and without exudation and injection of the submucosal vessels. A section of the abnormal portion of the duodenum revealed superficial destruction of the villi with no evidence of reaction. The margin of perforation showed a clean punched-out edge and no vascular reaction.

The detailed illustrative protocols of this section of the investigation lead to the following conclusions: In doses of approximately from 1 to 5 cg. per kilogram, pilocarpine does not produce gastric lesions; in doses of 5 cg. per kilogram or over, this drug causes acute erosions of the cardia and pylorus, which may be demonstrated both grossly and microscopically. Occasionally, similar lesions occur in the duodenum. Injections of from 5 to 7 cg. per kilogram of pilocarpine are toxic and produce extreme symptoms of secretion in the bronchi, respiratory distress and decreased heart rate. Rabbits receiving such large injections died within two hours of edema of the lungs.

WILL THE LESIONS BECOME CHRONIC?

In order to determine whether the lesions induced by pilocarpine may become chronic rabbits were given large doses of pilocarpine, which previously had been shown to produce lesions, and when these animals were in a very toxic state and likely to die sufficient atropine was given to neutralize the effects of the pilocarpine. From the illustrative experiments bearing on this point, it may be concluded that gastric lesions may still be present after one day. If lesions had been induced in these animals, and there is no reason to doubt it, these experiments show the remarkable tendency of such lesions to heal.

EXPERIMENT 11.—A male rabbit, weighing 1.9 Kg., that had been fed previously on cabbage received injections of pilocarpine as follows: 2:45 p. m., 0.5 cc. (5 per cent solution); 3 p. m., 1 cc., and at 3:30, 1 cc. At 3:50, it seemed positive that the animal would die soon. Accordingly, it was given 5 cc. of 2 per cent atropine hydrochloride solution subcutaneously, and this dose was repeated at 4. At 4:30, the animal's distress was relieved, salivation had ceased and the heart rate was 75 per minute. The next morning the animal refused food. In the afternoon, food was eaten. At 10 p. m. of the following day, the rabbit was killed.

Autopsy did not reveal any lesions of the stomach or intestinal tract. The lungs were normal.

EXPERIMENT 12.—A female rabbit, weighing 1.8 Kg., that had been fed on cabbage received 5 per cent solution of pilocarpine as follows: 2:50 p. m., 1 cc.; 3:10, 1 cc., and 3:30, 1 cc. The condition of the animal at 4:20 was so desperate that 10 cc. of 2 per cent solution of atropine hydrochloride was administered subcutaneously. Within an hour, the animal was without visible signs of distress. The next day, at 10 a. m., the rabbit was killed. Autopsy revealed two lesions of the cardia near the constriction band; one was 15 by 4 mm., irregular, not very deep, with the base characteristically hemorrhagic and smooth; the other lesion was small, 3 by 2 mm., and similar in appearance to the first. The lungs were normal.

Microscopic section of the large lesion showed a characteristic erosion without evidence of vascular reaction, inflammation or hyperemia of adjacent tissue.

EXPERIMENT 13.—A male rabbit, weighing 1.9 Kg., that had been fed on cabbage, was treated as in experiment 12, receiving in all 15 cc. of pilocarpine and at a critical period (two hours) was given 10 cc. of 2 per cent atropine hydrochloride solution, which alleviated its distress. At the end of two days, the rabbit was killed. Autopsy did not reveal any lesions.

THE INFLUENCE OF PILOCARPINE AND EPINEPHRINE

In the following section may be found typical experiments with the combined effect of pilocarpine and epinephrine, that is, the simultaneous influence of parasympathetic and sympathetic influences on the production of lesions.

The experiments demonstrate that the results with combined action of pilocarpine and epinephrine are not more remarkable than with pilo-

carpine alone. Certainly there was no greater tendency to localization of lesions to any one area of cardia, pylorus or duodenum with the combination than with pilocarpine by itself. The action of epinephrine alone did not produce any lesions. The effect of epinephrine alone is not surprising since the influence of this substance on the stomach is depressant for secretion and peristalsis, and thus neither chemical nor mechanical factors would have an opportunity to act on the production of lesions.

EXPERIMENT 14.—A female rabbit, weighing 1.9 Kg., that had been fed previously cabbage and oats received injections as follows: pilocarpine, 0.5 cc. at 2:20 p. m.; epinephrine, 0.1 cc. at 2:35; pilocarpine, 1 cc. at 2:50; epinephrine, 0.1 cc. at 3:05, and pilocarpine, 1 cc. at 3:25. At 4:30 the animal was killed. At autopsy, ten of the usual lesions were found in the cardia, all oval and varying in size from 3 mm. to that of a pinhead. The intestines were normal. Microscopic sections were not made.

EXPERIMENT 18.—A male rabbit, weighing 1.9 Kg., that previously had been fed on oats and turnips received injections as follows: epinephrine, 0.2 cc. at 1:50 p. m.; pilocarpine, 1 cc. at 2:10; epinephrine, 0.2 cc. at 2:30; pilocarpine, 1 cc. at 2:50; epinephrine, 0.2 cc. at 3:10, and pilocarpine, 1 cc. at 3:20. The rabbit was killed at 4 p. m., and autopsy revealed two characteristic lesions in the fundus 2 by 1 and 2 by 1.5 mm. in size, and one in the pylorus measuring 4 by 3 mm. There were no lesions in the duodenum or intestines.

EXPERIMENT 21.—A male rabbit, weighing 1.7 Kg., that previously had been fed on oats, received the following injections: epinephrine, 0.1 cc. at 1:50 p. m.; pilocarpine, 0.5 cc. at 2:00; epinephrine, 0.2 cc. at 2:10; pilocarpine, 0.5 cc. at 2:20; epinephrine, 0.2 cc. at 2:30, and pilocarpine, 1 cc. at 2:40. The rabbit was killed at 3:20 p. m., and autopsy disclosed four small lesions in the pylorus; the largest was 2 by 1 mm., the smallest, pinpoint in size. These were grossly characteristic of the lesions previously produced. There were no lesions in the fundus, duodenum or remainder of the intestines.

EXPERIMENT 22.—A male rabbit, weighing 1.8 Kg., that previously had been fed cabbage received epinephrine as follows: 0.2 cc. at 2 p. m.; 0.2 cc. at 2:20; 0.2 cc. at 2:40; 0.2 cc. at 3; 0.2 cc. at 3:20, and 0.2 cc. at 3:40. The rabbit was killed at 4 p. m. The stomach was greatly dilated. Lesions were not present in either the stomach or the intestines.

THE INFLUENCE OF ACIDITY ON THE PRODUCTION OF GASTRIC LESIONS WITH PILOCARPINE

In the course of this investigation it was noted that the type of food eaten apparently influenced the number of lesions found in the stomach. Diets of cabbage alone were usually followed by numerous cardiac, pyloric and occasionally duodenal lesions. Diets of oats and cabbage were productive of the same type of lesions, but fewer in number.

It is probable that these foods would tend to affect the acidity of the gastric contents so that high protein oats combining with acid would leave less free hydrochloric acid, and the low protein vegetable not com-

binning with as much hydrochloric acid would leave a greater free hydrochloric acid acidity.

For purposes of analysis of the contents of the rabbit's stomach, it was found to be impossible to withdraw anything with a stomach tube even though much water was introduced by tube. An approximate analysis, therefore, was made of the contents of the stomach removed immediately after death. Five grams of this material was diluted with distilled water and titrated with tenth normal sodium hydroxide against Töpfer's indicator to estimate free hydrochloric acid and against phenolphthalein to estimate combined hydrochloric acid. The results are expressed as acidity per hundred grams of food material. It is realized that these results are crude at best, but the differences are so striking as to serve the purpose of the inquiry.

The plan of the experiment to show the influence of acidity is as follows: Rabbits were selected in pairs, each pair having received the same amount of food, either oats or cabbage, for three days prior to the experiment. At the beginning of the experiment, one rabbit of the pair was given 1 or 2 Gm. of sodium carbonate in solution by stomach tube. Then both rabbits received injections of from 2.5 to 5 cc. doses of pilocarpine at twenty minute intervals, three or four times. When the toxic effect of the drug became pronounced in one or both of the animals, the pair were killed and immediate autopsy and gastric analyses performed. Typical results follow.

EXPERIMENT 23.—A male rabbit 23, weighing 2.4 Kg., and a male rabbit 24, weighing 2.5 Kg., had been fed oats for three days previous to the experiment. At 10 a. m., rabbit 23 received 50 cc. of 2 per cent sodium carbonate solution by sound.

Both animals received 0.5 cc. of pilocarpine subcutaneously at 10:10 a. m.; 1.0 cc. at 10:30 and again at 10:50. At 11:20, rabbit 24 was in marked respiratory difficulty. The other animal was also exhibiting symptoms, but not to the same degree. Both rabbits were killed at 11:30.

Rabbit 23: The contents of the stomach weighed 120 Gm.; free hydrochloric acid was 0, and total hydrochloric acid, 0. Lesions were not present in the stomach, duodenum or intestines.

Rabbit 24: The contents of the stomach weighed 119 Gm.; free hydrochloric acid was 50, and total, 90. Two lesions were present in the cardia, 2 by 3 mm., and 2 by 1 mm. There were two hemorrhagic areas the size of a pinpoint in the pylorus with slight loss of substance over them. Microscopic sections of the lesions showed characteristic superficial erosions of the mucous membrane with no vascular reaction in the rest of the mucosa or in the submucosa.

EXPERIMENT 24.—Both animals were fed on cabbage for three days. A male rabbit 25 weighed 2.2 Kg., male rabbit 26 weighed 2.5 Kg.

Rabbit 25 received 2 Gm. of sodium carbonate in 2 per cent solution at 9 a. m.

Both rabbits were given 0.5 cc. of 5 per cent pilocarpine solution at 9:10 a. m.; 1 cc. at 10, and 1 cc. at 11.

Respiratory difficulty was marked in both animals at 11:15. They were killed at 11:30. The stomachs of both were contracted and were filled with coarse bulky material of the same consistency.

Rabbit 25: The contents of the stomach weighed 113 Gm.; free hydrochloric acid was 0, and total, 0. Lesions were not found in the stomach or the duodenum.

Rabbit 26: The contents of the stomach weighed 108 Gm.; free hydrochloric acid was 130, and total, 180.

There were numerous pinpoint-sized hemorrhagic areas all over the cardia and eighteen lesions of varying size around the contraction ring, the largest 5 by 4 mm., and the smallest, 2 by 1 mm. There was also one small pyloric lesion, 4 by 2 mm., on the greater curvature near the pyloric valve. Duodenal or intestinal lesions were not found.

EXPERIMENT 25—Both animals received an oat diet for three days previous to the experiment. Male rabbit 27 weighed 1.8 Kg.; male rabbit 28 weighed 2.3 Kg.

At 9:40 a. m., rabbit 27 received 2 Gm. of sodium carbonate in 2 per cent solution by sound.

Both animals were given 0.5 cc. of pilocarpine at 9:45 a. m.; 1 cc. at 10, and 1 cc. at 10:20. They were both in great respiratory distress at 11 o'clock and were killed at 11:15.

Rabbit 27: The contents of the stomach weighed 100 Gm.; free hydrochloric acid was 0, and total, 0. Lesions were not found in the stomach, duodenum or intestines.

Rabbit 28: The contents of the stomach weighed 110 Gm.; free hydrochloric acid was 70, and total, 120.

There were two large hemorrhagic erosions in the cardia on either side of the greater curvature just above the contraction band, one 8 by 3 mm., and the other 10 by 5 mm. with irregular edges. There were two other small lesions in the cardia, one 2 by 3 mm., and the other 2 by 1 mm. Sections were not made. Grossly, these lesions were characteristic.

EXPERIMENT 26.—Both animals received a diet of cabbage for three days. Male rabbit 29 weighed 2.2 Kg., male rabbit 30 weighed 2.3 Kg.

Rabbit 30 was given 2 Gm. of sodium carbonate in 2 per cent solution by sound at 11 a. m. Both rabbits received 0.5 cc. of pilocarpine solution at 11:05 a. m.; 1 cc. at 11:30, and 1 cc. at 1 p. m.

The condition of the animals was such that they were killed at 1:20.

Rabbit 29: The stomach was in hour-glass contraction of the pyloric region, an unusual observation. The contents of the stomach weighed 75 Gm.; free hydrochloric acid was 80, and total, 120.

There were six pyloric lesions. Five of these had the gross appearance of erosions commonly found and varied in size from 3 by 1 mm. to 1 by 1 mm. On the greater curvature of the pylorus, 3 cm. above the pyloric valve, was a transverse lesion 15 by 6 mm. in size. This appeared different from any lesion thus far produced by the action of pilocarpine. Grossly, it was a punched-out area with straight sides, with no undermining or induration, extended through the entire mucosa, and showed muscularis as a base across which several vessels lay exposed with very little evidence of hemorrhage.

Microscopic section of this lesion showed the mucosa and submucosa to be absent. There were no undermining of the edges of the lesion, but in the angles of the edges and in the wall of the floor was a slight infiltration with poly-

morphonuclear cells. The whole appearance of the lesion was so unusual that it was regarded as a preexistent lesion.

Rabbit 30: The contents of the stomach weighed 106 Gm.; free hydrochloric acid was 30, and total, 70.

The reaction in this stomach even after the administration of alkali was acid. There was one small cardiac erosion near the contraction band, 1 by 1 mm. in size. There was no pyloric, duodenal or intestinal lesions.

EXPERIMENT 27.—Both animals had been fed cabbage for three days. Male rabbit 31 weighed 2.5 Kg., and male rabbit 32 weighed 2.5 Kg.

Rabbit 31 was given by sound 2 Gm. of sodium carbonate in 2 per cent solution at 10:30 a. m. Both animals received 0.5 cc. of pilocarpine at 10:35; 1 cc. at 11:10; 1 cc. at 1 p. m., and 1 cc. at 1:30. The animals were killed at 2:10.

Rabbit 31: The contents of the stomach weighed 80 Gm.; the free hydrochloric acid was 40, the total, 55.

There were two small erosions in the cardiac portion of the mucosa, 4 by 1 mm., and 3 by 2 mm. in size. There were no other gastro-intestinal lesions.

Rabbit 32: The contents of the stomach weighed 103 Gm.; the free hydrochloric acid was 130, the total, 160.

There were six erosions of the mucous membrane of the fundus; the largest, 3 by 3 mm., the smallest, 1 by 1 mm. There was one pyloric lesion, 4 by 2 mm. in size, and numerous small hemorrhagic areas in the duodenum. The remainder of the intestinal tract was normal.

From these experiments it is concluded that the quantity of free hydrochloric acid in the stomachs of the rabbits that had been given pilocarpine varied with the character of the food eaten. Irrespective of the character of the food, if the contents of the stomach were alkaline owing to alkali administration, lesions were not produced by pilocarpine given in quantities which induce lesions when the contents of the stomach remain acid. With the contents of the stomach acid the number of lesions produced seems to be somewhat proportional to the degree of free acid present.

EFFECTIVE AGENT IN THE PRODUCTION OF GASTRIC LESIONS WITH PILOCARPINE

Although the conclusions in the last section explain the rôle of acid in the formation of the lesions found in the stomach of rabbits after injection of pilocarpine, it does not clarify the mechanism by which pilocarpine causes formation of these lesions.

There are at least three questions that appear worthy of consideration in this problem.

1. Is the reaction of the contents of the stomach in itself sufficient for the production of the lesions?
2. Is the erosion a subsequent manifestation of an initial lesion brought about by changes in the circulation due to the action of the drugs used in the experiment?

3. Is the change in the circulation brought about by spasm of the terminal arteries due to vasomotor stimulation or through compression of the same vessels from increased tone of the muscularis mucosa due to parasympathetic stimulation?

Further studies were made in consideration of these points of view. The frequency with which lesions were visible from the exterior of the stomach at autopsy suggested the study of their formation by direct observation after an operative laparotomy. The details of such experiments follow.

PLAN OF EXPERIMENTS

The rabbit was placed on its back on a rabbit board and the fur shaved from the entire abdomen. Local anesthesia was induced with 1 per cent procaine hydrochloride solution by injection along anatomic planes as the operation progressed. The tissues were cut through by median incisions from the uppermost and lowermost angles, and appropriate lateral incisions were made so that finally the entire abdominal cavity covered by the peritoneum was exposed. Anesthesia of the peritoneum was produced by brushing 1 per cent procaine hydrochloride solution over the exposed subperitoneal tissue. The median incision of the peritoneum was followed by the continuation of the incisions above and below on one side only, the flaps thus made being carefully turned outward and the exposed peritoneal surface painted with 1 per cent procaine hydrochloride solution. The animal was so well anesthetized that it was not at all restless. A thin gauze wet with warm physiologic sodium chloride solution was packed along the lateral abdominal wall. The free edges of the abdominal flap were next fastened to the edge of the operating board and the excess gauze laid over it. Into this gauze the intestines were gently massed and protected while the flap on the other side of the abdomen was prepared and fastened, allowing the free margin of the gauze containing the intestines to be packed similarly along the opposite lateral wall, the intestines now being covered and included between the packings. With caution, this procedure was painless. Over the thin packing of the intestines, thick warm saline gauze was laid which could easily be removed for inspection of the intestines.

The liver was then carefully raised and the stomach brought forward so that a good view of the organ from cardia to pylorus and the upper part of the duodenum was possible. The organ was packed in position with warm saline gauze. The peritoneal covering of the stomach was kept continuously moist with warm physiologic sodium chloride solution, and when not under observation was covered with warm moist gauze. The effect of the local anesthetic continued for a period of from three to three and one-half hours. By this technic, the course of the vessels in the stomach was clearly recognized, and that of the superior circumflex artery was especially to be discerned by means of a hand lens. Accompanied by vena comitantes, branches of the superior circumflex artery course for a short distance in the subserosa whence they give off branches to the serosa and then continue still in the serosa with numerous branchings to within 3 cm. of the greater curvature. At the termination of these vessels and also of their branches, the small end arterioles suddenly pierce the muscularis propria into the submucosa. Further tracing of the vessels is not possible from the exterior. This detailed explanation is given for the better understanding of subsequent discussions.

ILLUSTRATIVE EXPERIMENTS

EXPERIMENT 28.—Laparotomy was performed on a rabbit, weighing 2.5 Kg., that had been fed on cabbage, the operation being completed at 3 p. m. The stomach was full and quiescent. From 3 o'clock until 4:25 only two peristaltic waves were seen to pass over the surface of the stomach. The duodenum and intestines were more active, one peristaltic wave passing every twenty minutes.

At 4:30, 0.5 cc. of 5 per cent solution of pilocarpine was injected subcutaneously. Within five minutes, vigorous peristaltic waves arising in the cardia were passing over the stomach at twenty to thirty second intervals. At 4:35, 1.0 cc. of 5 per cent solution of pilocarpine was injected intramuscularly into the anterior cardiac wall of the stomach. A second similar injection was given subcutaneously at 4:50. Following this injection, the strength of peristalsis diminished. At 5:05, bronchial râles were heard, and shortly afterward the whole stomach became markedly cyanotic. At 5:11, a small, round gray area, the size of a large pinhead appeared on the anterior wall of the cardia. This area, viewed with a hand lens, was evidently not in the muscularis propria, but probably in one of the innermost tissue layers of the organ. There was no relation of this lesion to any of the terminal arterioles that pierced the muscularis propria. At the same time, there was no relation of this to the site of injection of pilocarpine which had been made directly into the pylorus musculature. At 5:20, 1 cc. of pilocarpine solution was injected subcutaneously. The stomach was continually active, and respiratory difficulty was now marked; the cyanosis of the stomach was very noticeable. A dark hemorrhagic center gradually appeared in the middle of the gray area, which slowly increased in size as the lesion developed. Several similar areas developed also on the anterior wall of the cardia. No lesion developed at the site of the injection of pilocarpine. The rabbit was killed at 6 p. m. The contents of the stomach weighed 113 Gm.; the free hydrochloric acid was 130, and the total, 180.

On the cardiac portion of the mucosa were sixteen small erosions. There were two erosions of the pyloric mucosa, 3 by 2 mm. and 1 by 1 mm. in size, but not related to the site of the direct injection of pilocarpine, which was marked by slight hemorrhage into the muscular layers and visible by transmitted light. Numerous fine pinpoint-sized hemorrhages occurred in the duodenum with slight loss of substance at the site of the lesion.

EXPERIMENT 31.—Laparotomy was completed at 10:30 a. m., on a male rabbit weighing 2.2 Kg., and the stomach was observed for one hour. The stomach was full and not contracting. At 11:30, 0.5 cc. of 5 per cent solution of pilocarpine was injected subcutaneously. Salivation and gastric peristalsis began almost simultaneously three minutes after injection, and the latter became well established at the rate of three to four waves per minute. At 11:40, 0.5 cc. of the pilocarpine solution was injected into the submucosa of the cardia. At 12, 1 cc. of 5 per cent solution of pilocarpine was injected subcutaneously, causing a decrease in salivation and slowing gastric peristalsis rate to two to three per minute. However, the waves seemed stronger. At 12:05 p. m., bronchial râles were heard and respiratory difficulty was evident. The stomach became cyanotic and at 12:15, isolated gray areas were noted along the greater curvature. At 12:30, 1 cc. of pilocarpine solution was injected subcutaneously. The gray areas in the organ slowly increased in size and developed hemorrhagic centers. As in previous experiments, lesions were not associated with direct injection of pilocarpine into the stomach, and no areas indicating lesions were related to the terminal branches of the external vessels which pierced the muscularis propria.

At 1 p. m., the stomach was markedly cyanotic, and the animal was killed. Numerous lesions were present in the fundus, varying in size from that of a pinpoint to 4 by 8 mm. Microscopically, these lesions were erosions of the mucosa and even very small lesions, which were occasionally met with, showed slight superficial sloughing of cells with no vascular reaction in the surrounding tissue. Two small hemorrhagic areas, 1 by 2 mm., and 1 by 1 mm. in size, were found in the pylorus. There were no duodenal or intestinal lesions. The contents of the stomach weighed 104 Gm., the free hydrochloric acid was 40, total, 140.

EXPERIMENT 32.—Laparotomy was performed on a male rabbit weighing 2.3 Kg. that previously had been fed cabbage. The operation was completed at 11 a. m. The stomach was quiescent and peristaltic movements were not observed up to 11:20, when 0.1 cc. of epinephrine solution was injected intravenously. Contractions were not visible for the next twenty minutes. At 11:40, 0.5 cc. of 5 per cent solution of pilocarpine was injected subcutaneously. Salivation and gastric peristalsis were evident within three minutes, and in ten minutes, waves were passing over the stomach at the rate of five to six a minute. At 11:45, 0.5 cc. solution of pilocarpine was injected directly into the submucosa of the stomach on the anterior wall of the fundus. At 12, 0.1 cc. of epinephrine solution was injected intravenously. Contractions for the next twenty minutes remained as before. At 12:20 p. m., 0.5 cc. of pilocarpine solution was injected subcutaneously. Gastric contractions slowed to two or three per minute. At 12:40, 0.2 cc. of epinephrine was injected intravenously. At 1, 1.0 cc. of pilocarpine was administered subcutaneously, and slow but strong contraction, two to three per minute, continued. One small gray area (anemic area?) developed on the anterior surface of the cardia, and this gradually increased in size and developed a hemorrhagic center. The rabbit was killed at 1:20.

There were two pyloric lesions, 8 by 4 mm. and 2 by 1 mm. in size. Numerous hemorrhagic areas were present on the cardiac portion of the stomach, varying in size from that of a pinpoint to 2 by 3 mm. Duodenal or intestinal lesions were not present. There was no lesion associated with the site of the direct injection of pilocarpine.

EXPERIMENT 33.—Laparotomy was performed on a male rabbit weighing 2.5 Kg. that previously had been fed on cabbage. The procedure was completed at 3 p. m. The stomach was full and quiescent, only two peristaltic waves passing over the organ in an hour. At 4 o'clock a small fistula was made in an area free from large vessels on the anterior wall of the cardia near the greater curvature. Five grams of the contents of the stomach was removed for analysis. It showed free hydrochloric acid, 130; total hydrochloric acid, 175.

The remainder of the contents of the stomach was carefully removed, 117 Gm. in all. A two-way catheter was inserted in the fistula and fastened in place with a purse-string suture through the entire wall. By means of this catheter, the stomach was kept full of, and continuously washed with, warm 0.5 per cent sodium bicarbonate solution.

At 4:40, 0.5 cc. of 5 per cent pilocarpine solution was injected subcutaneously. Within three minutes, salivation and gastric peristalsis occurred. At 5 o'clock, 0.5 cc. of pilocarpine solution was again injected subcutaneously, without causing any change in the condition of the animal. At 5:20, 1 cc. of pilocarpine was given subcutaneously. Gastric contractions were vigorous, two or three per minute. Areas of anemia were not visible from the outside. At 5:40, 1 cc. of pilocarpine was again injected subcutaneously. At 6 o'clock, the rabbit was killed.

Lesions were not present in the pylorus, duodenum or intestines. In the cardia were hemorrhagic areas radiating from the incision for insertion of the tube into the fistula. These areas were apparently the results of clots in the vessels from the trauma, and erosion over them was not evident.

These experiments lead to the following conclusions:

1. The acidity in the stomach of the rabbit is not markedly different before and after injection of 5 per cent solution of pilocarpine (experiments 33 and 28). Therefore it is improbable that change in acidity is responsible for the formation of lesions in these experiments.

2. Lesions are produced in the cardia in greatest numbers, and to a less extent in the pylorus and duodenum by subcutaneous injection of pilocarpine. Injection of pilocarpine solution directly into the submucosa or muscularis propria did not produce any lesions at the site of injection whether the solution injected was weak (experiment 31) or strong (experiment 28).

3. A most remarkable effect of injections of pilocarpine is the great increase in gastric peristalsis.

4. The appearance of lesions is related to the development of cyanosis of the stomach, which in turn closely follows the respiratory difficulty due to pulmonary edema and diminished heart rate.

5. There is no apparent relationship between the lesions and the points of entrance of small branches of the epigastric arteries which could be seen to pierce the muscularis propria to supply the mucosa and submucosa.

6. The "anemic" or gray areas were not visible through the wall of the stomach in the absence of bulky material and hydrochloric acid. If these lesions were due to localized areas of constriction of muscularis mucosa or to spasm of terminal arterioles, would they not occur whether superficial mucosal erosions were formed over them or not?

7. It would appear that anemia of the localized area, associated with cyanosis, and the subsequent action of the gastric juice on this local anemic area lead to the development of these acute lesions.

EXPERIMENTS WITH OTHER ANIMAL SPECIES

To determine whether the development of acute lesions is common to all animals under the influence of pilocarpine, experiments have also been carried out with the rat, cat and guinea-pig.

EXPERIMENTS WITH ALBINO RATS

The nature of the stomach and the contents of the stomach of this animal is very different from that of the rabbit. In the rat, the esophagus enters into the lower end of a pouch which is capable of considerable distention, and is directly continuous with the stomach proper, the muscular layers of which begin

abruptly and continue to the pylorus. The mucosa over the muscular layers is thrown into low thick folds which do not definitely divide the stomach into pyloric or cardiac mucosa. In fact, the cardiac portion is a pouch, and the pyloric division is a muscular organ, the mucosa of which resembles the cardiac mucosa in the rabbit. There is no smooth area of mucosa corresponding to the pyloric area in the rabbit.

The nature of the contents of the stomach is different from that of the rabbit also. It is semifluid in consistency and its quantity was never sufficient for gastric analysis. Qualitatively it always contained considerable free hydrochloric acid.

All ten experiments were made with albino rats with a variety of doses of pilocarpine. No definite lesions could be discovered in the stomach, duodenum or intestine of the rat as the result of the administration of pilocarpine. Illustrative experiments are appended.

EXPERIMENT 37.—A female rat weighing 340 Gm. received the following subcutaneous injections of a 5 per cent solution of pilocarpine: 0.2 cc. at 10 a. m.; 0.3 cc. at 10:30, and 0.3 cc. at 11.

The usual symptoms of toxicity appeared, and the rat was killed at 11:30. Lesions were not present in the gastro-intestinal tract.

EXPERIMENT 41.—A rat weighing 250 Gm. received the following subcutaneous injections of a 5 per cent solution of pilocarpine: 1.0 cc. at 2:30 p. m., and 0.5 cc. at 3.

The animal died at 4 o'clock. Autopsy did not show any lesions of the gastro-intestinal tract.

EXPERIMENT 45.—A rat weighing 291 Gm. received the following subcutaneous injections of a 5 per cent solution of pilocarpine: 1 cc. on March 3, 1926, at 4:15 p. m.; 0.6 cc. on March 4, at 11:40 a. m.; 0.6 cc. on March 5, at 11:20 a. m.; 0.6 cc. on March 6, at 11:40 a. m.; 0.6 cc. on March 8, at 11:15 a. m.; 0.6 cc. on March 9, at 11:10 a. m.; 0.6 cc. on March 10, at 10:30 a. m.; 0.6 cc. on March 11, at 10:25 a. m. and 0.6 cc. on March 12, at 10:55 a. m.

The animal was killed on March 12 at 11:30 a. m., and immediate autopsy did not reveal any lesions.

EXPERIMENTS WITH CATS

In the cat, pilocarpine produced in addition to the usual symptoms of lacrimation, salivation, râles and diarrhea, marked contraction of the pupil and frequent vomiting.

In our experience with cats, pilocarpine failed to induce lesions in the gastro-intestinal canal.

Illustrative examples follow.

EXPERIMENT 47.—A male cat, weighing 3.2 Kg., fed on a meat diet received subcutaneous injections of 0.5 cc. of a 5 per cent solution of pilocarpine at 9 a. m. and again at 9:30. Ten minutes after the first injection, the toxic symptoms, salivation, diarrhea and contraction of pupil, occurred. Five minutes after the second injection, the animal vomited 10.5 cc. of semifluid gastric contents, which showed free hydrochloric acid, 35, and total hydrochloric acid, 80. At 10:30, and again at 11:30, 1 cc. of pilocarpine solution was injected. The animal died at 7 p. m. Autopsy showed the stomach to be empty. There were no lesions throughout the alimentary tract.

EXPERIMENT 48.—A male cat, weighing 2.4 Kg., received the following subcutaneous injections of a 5 per cent solution of pilocarpine: 0.5 cc. at 2 p. m., 1 cc. at 2:30, 1 cc. at 3 and 1 cc. at 4.

The animal vomited six times within one hour after the first injection. Analysis of the vomitus at 2:24 p. m. showed a content of free hydrochloric acid of 28 and a total acidity of 60. Analysis of vomitus at 2:45 revealed free hydrochloric acid content of 30 and total hydrochloric acid of 72.

Respiratory difficulty was marked at 3 o'clock. Death occurred at 6:20. Immediate autopsy did not reveal any lesions in the gastro-intestinal tract.

EXPERIMENT 49.—A female cat weighing 1.6 Kg., that had been fed with meat four hours previously was used. A stomach tube was passed, and 20 cc. of gastric juice was obtained. Analysis showed free hydrochloric acid, 21, and total hydrochloric acid, 64.

Pilocarpine in 5 per cent solution was then injected subcutaneously as follows: 0.5 cc. at 12 o'clock, 1. cc. at 12:30 p. m., and 1 cc. at 1.

The animal vomited three times, and the last vomitus contained free hydrochloric acid, 24, and total hydrochloric acid, 60.

The animal was killed at 6 p. m. There were no lesions in the gastro-intestinal tract.

EXPERIMENTS WITH GUINEA-PIGS

The stomach of the guinea-pig is similar to that of the rabbit. Its contents differ from those of the rabbit in possessing a relatively low acidity and in being more fluid.

Pilocarpine injected subcutaneously into the guinea-pig produced lesions of the gastric mucosa which, microscopically, are unlike the lesions induced by pilocarpine in the rabbit. Those in the guinea-pig resemble the type of lesion found when intestinal hemorrhage is produced in dogs by Witte's Peptone.⁶

The smallest lesion produced by pilocarpine in the rabbit showed a distinct loss of superficial mucous membrane. With the guinea-pig, the lesions consist of superficial capillary dilatation without erosion or loss of substance.

Whether mechanical or chemical factors influence the change in the character of the lesions is undetermined.

Illustrative experiments follow.

EXPERIMENT 50.—A guinea-pig, weighing 400 Gm., previously fed cabbage and carrots, received subcutaneous injections of a 5 per cent solution of pilocarpine as follows: 0.2 cc. at 10:30 a. m., and 0.2 cc. at 11.

The symptoms of toxicity due to the pilocarpine were pronounced at 11:30 when the animal was killed.

Immediate autopsy revealed two hemorrhagic areas irregular in size on the mucosa of the cardia. They resembled an intense coloration without any loss of substance, one 6 by 3 mm., the other 4 by 3 mm. in size. Microscopic sections of these areas showed the mucosa to be intact. In the stroma of the villi in the area of the lesion, the superficial capillaries were tremendously dilated, and in areas near the surface a few ruptured vessels were seen. In the fundal portion of the mucosa, there were a few dilated vessels.

EXPERIMENT 51.—A guinea-pig of 400 Gm., fed on cabbage, received subcutaneous injections of pilocarpine as follows: 0.2 cc. of 5 per cent solution of pilocarpine at 10:28 a. m., and 0.3 cc. at 10:50.

At noon, this pig was in a very toxic condition and was killed. At autopsy, four lesions were found on the cardiac mucosa, 8 by 4 mm., 4 by 2 mm., 7 by 2 mm., and 3 by 1 mm. in size. Microscopic section revealed that the lesions consisted chiefly of superficial capillary dilatation without erosion or loss of tissue.

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EXPERIMENT 52.—The preceding experiment was repeated with a guinea-pig weighing 410 Gm., except that a greater time interval was allowed to elapse between the last injection and the autopsy. Pilocarpine in 5 per cent solution was injected subcutaneously as follows: 0.3 cc. of pilocarpine solution at 10:30 a. m., and 0.3 cc. at 11. The animal was killed. At autopsy four lesions were present, 12 by 8 mm., 9 by 3 mm., 4 by 2 mm., and 4 by 1 mm. in size. Microscopic section revealed lesions of the character already described in experiments 50 and 51.

EXPERIMENT 53.—In this experiment an attempt was made to increase the acidity of the gastric content by passage of 10 cc. of tenth normal hydrochloric acid through a small sound into the stomach. The guinea-pig weighing 400 Gm. was then given subcutaneous injections of a 5 per cent pilocarpine solution as follows: 0.3 cc. at 10 a. m.; 0.3 cc. at 10:30, and 0.3 cc. at 11.

The animal was killed at 1 p. m. The small quantity of gastric juice was distinctly acid with Töpfer's reagent. There were three hemorrhagic areas on the cardiac mucosa of the stomach, 6 by 4 mm., 5 by 2 mm., and 3 by 1 mm. in size. Microscopic section of these lesions showed the mucosa to be intact and the superficial capillary distention to be the most prominent feature of the lesion.

SUMMARY OF CONCLUSIONS

1. Pilocarpine injected subcutaneously into rabbits in toxic doses will produce lesions of the mucous membrane of the stomach and, occasionally, of the first portion of the duodenum.
2. Pilocarpine injected subcutaneously with alternating intravenous doses of epinephrine will produce similar lesions, the nature and location of which differ little from those produced by pilocarpine alone.
3. Epinephrine injected intravenously does not produce lesions in the gastro-intestinal tract of rabbits.
4. The lesions produced do not become chronic.
5. The character of the food eaten previous to the injection of pilocarpine apparently influences the number of lesions produced in rabbits. When the food has a high protein content, fewer lesions are found than when the protein content is relatively low.
5. Free acidity influences the formation of gastric lesions in the rabbit under the experimental conditions. Relatively high acidity which is associated with food of a low protein content causes more lesions than low acidity which is related to food with a high protein content. The absence of acidity, due to the administration of alkali, evidently removes the predisposing cause of the erosion.
6. The variation in acidity in the stomach of the rabbit before and after the injection of pilocarpine, when the animal has been fed cabbage is not marked. It is improbable, therefore, that change in acidity alone is responsible for the formation of lesions.
7. The most pronounced influence of pilocarpine in the stomach of the rabbit is the great increase in peristalsis. This effect, together with

the bulky coarseness of the contents of the stomach and its acidity, suggests a mechanical-chemical factor in the formation of lesions.

8. The appearance of lesions is related to cyanosis of the stomach, which in turn closely follows the respiratory difficulty due to pulmonary edema and diminished heart rate.

9. There is no apparent relationship between the lesions and the points of entrance of small branches of the epigastric arteries which can be seen to pierce the muscularis propria to supply the mucosa and the submucosa.

10. The "gray" or "anemic" areas are not visible through the wall of the stomach in the absence of gastric contents. If these lesions are due to localized areas of constriction of muscularis mucosa or to spasm of terminal arterioles, would they not occur whether superficial mucosal erosions were found over them or not?

11. It would appear that anemia of localized areas, associated with cyanosis of the entire stomach, and the subsequent action of the gastric contents on this local anemic area lead to the development of these acute lesions.

12. Pilocarpine injected subcutaneously into the cat and the rat does not produce lesions of the stomach and the intestines.

13. Pilocarpine injected subcutaneously into the guinea-pig produces lesions which microscopically do not resemble those produced in rabbits, but appear to be related to an apparently different type of phenomenon.

14. The results of this investigation indicate that the action of pilocarpine in the production of lesions is not specific, but is a species peculiarity.

TOXIC ANEMIA PRODUCED BY CLOSTRIDIUM WELCHII *

MARJORIE B. PATTERSON

AND

LUDWIG KAST, M.D.

NEW YORK

The significance of intestinal microbes in physiology and pathology still remains rather obscure. The obvious general injury in conditions such as botulism, dysenteries, enteric fevers and inflammations of the coats of the appendix as well as in acute intestinal inflammations of infants are well known. The possible importance of intestinal microbes in more insidious pathologic processes is not so convincingly demonstrated and has long been a subject of theoretical controversy. More recently, Moody and Irons ¹ as well as Coates ² (1923) considered that abrasions or ulcerations of the mucous membrane may permit bacteria or their toxic products to enter the blood stream. In 1901, Hunter ³ ascribed pernicious anemia to absorption of toxic products from the intestine, and this theory has received much support. In 1926, Koessler ⁴ suggested that such absorption may be facilitated by epithelial changes in the intestinal lining, possibly due to vitamin deficiency.

The fact that intestinal bacteria may penetrate the intestinal lining and enter the blood stream without visible ulceration has been generally accepted since 1895, when Nocard ⁵ demonstrated the correlation between ingestion of food and the presence of bacteria in the blood of animals. Reith ⁶ has recently studied the question anew. He found bacteria in 84 per cent of blood specimens and in 83 per cent of specimens of muscle from healthy swine, rabbits and guinea-pigs. Strict anaerobes were found in 49 per cent of the specimens of muscle and in 39 per cent of the specimens of blood. In fasting animals the blood still

* From the Department of the Laboratories, New York Post-Graduate Medical School and Hospital.

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harbored these anaerobic bacteria. Observations of this sort again serve to emphasize the importance of the intestinal lumen as the source of abundant and various microbes and their products.

The sporogenic anaerobic bacteria of the intestinal tract have excited renewed interest as a result of the work of Weinberg and Seguin,⁷ Heller,⁸ Hall⁹ and Kahn.¹⁰ These workers have described the gross lesions in animals, largely with a view to rapid bacteriologic diagnosis and recognition of species. Attempts to produce chronic disease similar to a human pernicious anemia have been recorded by Torrey and Kahn. Much obscurity still remains in this field.

PRELIMINARY EXPERIMENTS

The bacterial strains employed in the present study were obtained from human sources by the usual cultural methods and were finally isolated in pure culture by the Barber¹¹ single cell technic. As a preliminary test of toxicity, from 0.3 to 1.5 cc. of eighteen-hour anaerobic broth cultures were given by intramuscular injection into guinea-pigs. The results may be illustrated by a few selected examples.

GUINEA-PIG 157.—The animal, weighing 434 Gm., received an intramuscular injection into the thigh of 0.3 cc. of an eighteen-hour anaerobic dextrose broth culture of *Cl. edematiens*, strain I, and died in twelve hours. On examination six hours later, there was a moist area of skin at the site of injection, without loss of hair. A smear of the edematous muscle revealed large gram-positive rods, single or in pairs, containing oval central or subterminal spores. The subcutaneous tissue was thickened by red gelatinous edema extending from the thigh to the sternum, with gas bubbles in the inguinal regions. Smears of peritoneum showed bacilli in pairs and in filaments of from six to eight organisms, including beaded and citron forms, but without spores. A slightly fetid odor was present. The liver appeared normal, but smears from its surface contained many long, thick filaments. The gallbladder was empty; the intestines were injected and contained bile. The spleen, kidneys and suprarenals were congested. The abdominal and inguinal lymph nodes and the testes were hemorrhagic. Cultures of the heart blood were positive for *Cl. edematiens*.

Sections of the spleen showed moderate distention of the venous sinuses. In the liver there was an excessive phagocytosis of erythrocytes by the Kupffer

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cells. In the kidneys the glomeruli were congested and the glomerular tufts contained an excess of lymphocytes and polymorphonuclear leukocytes. The epithelium of the convoluted tubules was swollen but stained well. An occasional albuminous cast was seen in the collecting ducts.

GUINEA-PIG 155.—The animal, weighing 434 Gm., received an intramuscular injection of an eighteen-hour anaerobic broth culture of *Vibrio septique*, strain I. Death occurred in twelve hours. Examination five hours after death revealed moist skin with loss of hair and marked edema at the site of the injection. In the muscle here there were many bacilli, containing subterminal or occasional median oval spores, and a few filaments. The areolar connective tissue was swollen by deep rose, gelatinous edema and a smaller amount of thin serous fluid. Large gas pockets were observed in the inguinal regions. The liver appeared normal; the gallbladder was filled; the spleen and suprarenals were slightly congested as were many of the lymph nodes. The kidneys appeared normal. Bacterial filaments were found on the peritoneum and in the spleen, and culture of the heart blood gave characteristic growth of *Vibrio septique*.

Sections of the spleen revealed a marked hydropic swelling of the lining endothelium of the follicular arterioles and unusually abundant nucleated cells mingled with the blood in the venous sinuses. Erythrophagocytosis was not increased. Apparently the chief effect on the spleen was the loosening of vascular endothelium and reticular cells of the pulp. In the lymph nodes a similar swelling of the endothelium of the sinuses and marked congestion were recognized. In the liver there was also marked swelling of the endothelial lining of the sinusoids with granular degeneration and fragmentation of the hepatic cells. The nuclei remained stainable. The glomerular tufts of the kidney were congested and contained an excess of nucleated cells, chiefly lymphocytes and polymorphonuclear leukocytes. The epithelium of the convoluted tubules was swollen and sometimes fragmented, but the nuclei were well preserved. The suprarenal cortex was congested.

GUINEA-PIG 69.—The animal, weighing 400 Gms., received four intramuscular injections of cultures of *Cl. bifermentans*, strain 8. The first dose was 1.5 cc. of an eighteen-hour anaerobic dextrose broth culture. Seven days later, a precisely similar dose was given. After another interval of six days a third dose of 1.5 cc. of an eighteen-hour culture in cooked meat was given and six days later, on the twentieth experimental day, 1.5 cc. of a five-day culture in cooked meat medium. Death followed in three hours. Necropsy, performed at once, revealed marked congestion of the spleen, liver, kidneys, intestines and mesentery. The abdominal lymph nodes were swollen, soft and congested. Culture of the heart's blood remained sterile.

Histologic examination of the spleen showed moderate dilatation of the follicular arterioles and slight edema of the follicles. The pulp cords were somewhat thickened and there was abundant brown pigment within phagocytic cells in the pulp cords and in the sinuses. Phagocytes containing from one to four well preserved erythrocytes were fairly numerous. Phagocytosis of erythrocytes by the Kupffer cells was also found in the liver.

GUINEA-PIG 124.—The animal, weighing 375 Gm., was given one intramuscular injection of 1 cc. of an eighteen-hour anaerobic dextrose broth culture of *Cl. welchii*, strain 10. Death occurred in sixteen hours. Examination, four hours after death, showed the thigh muscle at the site of the inoculation soft and deep rose with a small amount of blood-stained serous fluid present. In this there were many large bacilli in threads of from eight to ten organisms. Capsules could not be demonstrated on them. The subcutaneous tissue con-

tained small gas bubbles in a rose colored serum extending over the abdomen to the axillary regions. The peritoneum was injected, but smears did not reveal any organisms. The kidneys and liver were slightly congested; the spleen was dark red. The mesenteric lymph nodes were hemorrhagic and the inguinal lymph nodes were unrecognizable in the disintegrated subcutaneous tissue. Culture of the heart's blood was positive for *Cl. welchii*.

Microscopic examination of sections of the spleen disclosed remarkable evidence of acute destruction of the blood. The splenic follicles were edematous and the follicular arterioles and capillaries moderately distended. The pulp cords were rich in red blood cells and many of these red cells were within phagocytes. In the venous sinuses almost half the erythrocytes were within phagocytic cells and as many as fourteen erythrophages containing from one to ten erythrocytes each were seen in the section of a single venous sinus. Small clumps of agglutinated red cells were also seen lying free within the sinuses. Ingested leukocytes were also found as well as nuclear fragments within the pulp cells, but phagocytosis of the white blood cells was evidently less active as compared with that of the red cells. In the liver, the hepatic columns and endothelium of the sinusoids were swollen, and the endothelial cells were loosened in part. Phagocytosis of from one to three erythrocytes by one of these endothelial cells was frequently seen. Many rounded areas of early focal necrosis were observed in the intermediate zone of the hepatic lobules. In the kidney, the glomerular tufts and the capillaries of the medulla were engorged, apparently because of mechanical obstruction by agglutinated and adherent erythrocytes. Extravasation of blood into the tubules was not recognized. The suprarenals showed many extravasated erythrocytes between the medullary columns. In the lymph nodes generally, there were diffuse edema and congestion with occasional examples of erythrophagocytosis by the lining endothelium of the smaller blood vessels. In the bone marrow, the blood vessels were engorged. The giant cells appeared as masses of faintly stained granular protoplasm containing deeply pyknotic nuclear fragments and in some instances phagocytized erythrocytes.

In determining the virulence of various strains of *Cl. welchii*, many guinea-pigs have been used and the protocols of these animals all show the marked blood destruction by toxic strains of this organism. When the animal died within sixteen hours after inoculation, capsules were ordinarily not recognized in the bacterial smears from the organs. In such cases, the edema was often of slight extent and gas was not found in the tissues. Marked congestion of the small intestine with bile in its interior with the empty gallbladder, described by Heller⁸ (1920) as a characteristic occurrence in guinea-pigs killed with *Vibrio septique*, have been observed in guinea-pigs dying quickly after injection with virulent *Cl. welchii*.

EXPERIMENTAL TESTS ON RABBITS

The marked destruction of the blood observed in these experimental animals inoculated with *Cl. welchii* suggested that this organism, which is so commonly found in the human intestine, might play a part in the secondary anemias associated with digestive disorders. It was therefore

decided to undertake a study of the toxic anemia produced by *Cl. welchii* in animals. Rabbits were chosen for this work because of the accessible ear veins. The suggestion that this organism may be related to pernicious anemia, offered by Herter many years ago, had received renewed attention in 1924, as the result of the work of Kahn,¹² and of Moench, Kahn and Torrey¹³ in 1925. The evidence of a specific causative relation of *Cl. welchii* to a particular type of human anemia did not appear convincing.

Adult male rabbits weighing from 5 to 6 pounds (2.3 to 2.7 Kg.) were injected intramuscularly or intravenously with varying amounts of whole culture or with bacteria-free toxic filtrates of *Cl. welchii*. With each type of inoculum an attempt was made to produce severe acute toxemia as well as a milder, more chronic disease. In the animals treated for long periods it was thought that something akin to the theoretical absorption of toxin, whether periodical or continuous, might be paralleled, so as to produce an experimental toxic condition which might simulate the chronic anemias of man, although even in these animals the experimental period was rather brief in comparison with the development period of chronic anemia in man.

For inoculations with whole cultures, eighteen-hour growth in anaerobic dextrose broth was employed. The toxic filtrates first employed were prepared and standardized by the method of Bull and Pritchett.¹⁴ In the later work, the method was modified by employing the broth formula of Kahn and Torrey¹⁵ and by neutralizing the supernatant culture fluid to p_H 7 before passage through the Berkefeld N filter. All the toxic filtrates were tested on pigeons by injection of from 0.3 to 1 cc. into the breast muscle, and only those which killed the pigeon within twenty-four hours were used in the experiments on rabbits. These toxic filtrates maintained their full potency at icebox temperature for ten days, but after this time there was a loss of toxicity while the hemolytic property tested in vitro by the method of Lyall began to decrease only after three or four weeks.

The culture strains of *Cl. welchii* were tested for virulence by injection of eighteen-hour anaerobic dextrose broth cultures into guinea-pigs to ascertain the dose required to kill the animal in from eighteen to

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14. Bull, Carroll G., and Pritchett, Ida W.: Identity of the Toxins of Different Strains of *B. welchii* and Factors Influencing Their Production in Vitro, *J. Exper. Med.* **26**:867, 1917.

15. Kahn, M. C., and Torrey, J. C.: A Pernicious Anemia-Like Blood Condition Produced in Monkeys with *B. Welchii* Toxin, *Proc. Soc. Exper. Biol. & Med.* **22**:8, 1925.

thirty-six hours. The ability to lake in vitro the red blood corpuscles of man, sheep, rabbit and guinea-pig was ascertained by Kahn's¹⁰ modification of Lyall's technic. For convenience the strains were then classified into four groups: (1) hemolytic and toxic; (2) toxic and non-hemolytic; (3) hemolytic and nontoxic, and (4) nonhemolytic and nontoxic. This grouping is not to be confused with that of Simonds, which is based on the ability of strains of *Cl. welchii* to ferment glycerol and inulin.

The blood of the rabbits was examined from time to time, the specimens being taken by puncture of an ear vein. The blood counts were all made by one person. The hemoglobin was estimated with the Dare instrument in which a reading of 100 per cent was equivalent to 13.7 Gm. hemoglobin per hundred cubic centimeters of blood. Blood films for differential count were stained with the tetrachrome stain of MacNeal.¹⁶ In some instances vital-stained preparations and peroxidase preparations were made.

ACUTE INTOXICATION OF RABBITS

Strains of group 1 produced severe intoxications in doses of from 0.5 to 1.0 cc. of whole culture or of from 1 to 10 cc. of bacteria-free filtrate. In the inoculated animals the erythrocytes dropped as low as 700,000 per cubic millimeter and the hemoglobin as low as 20 per cent, or 2.74 Gm. per hundred cubic centimeters. The record of rabbit 19, shown in chart 1, is typical of the behavior of these animals. The color index tended to rise, approaching 1 and in one instance reaching 1.42, whereas the original normal for these rabbits ranged from 0.56 to 0.80 with an average of 0.63. A leukocytosis, attaining at times 46,600 per cubic millimeter, occurred during the first ten days. Leukocytosis was not observed in every animal but was almost general.

Simpson¹⁷ gives as figures for normal rabbits, from 4,000 to 14,300 leukocytes per cubic millimeter. Bushnell and Bangs,¹⁸ as a result of their studies of normal rabbits, consider a white cell count above 15,400 per cubic millimeter as abnormal. In the present study, therefore, we have recognized a leukocytosis only when the count reached 15,000. A marked anisocytosis and poikilocytosis was present at the height of the toxemia. The degree of these changes is indicated in the protocols by symbols, varying from + — (very slight) to + + + + (very marked). A short time later an increase in polychromatophilic red cells

16. MacNeal, Ward J.: Tetrachrome Blood Stain; an Economical and Satisfactory Imitation of Leishmans' Stain, *J. A. M. A.* **78**:1122 (April 15) 1922.

17. Simpson, Miriam: The Experimental Production of Macrophages in the Circulating Blood, *J. M. Research* **43**:77, 1922.

18. Bushnell, L. D., and Bangs, Edna F.: A Study of the Variation in Number of Blood Cells of Normal Rabbits, *J. Infec. Dis.* **39**:291, 1926.

occurred, the maximum being 93,000 per cubic millimeter. Nucleated red cells, including normoblasts, macroblasts and microblasts, appeared in numbers ranging from 114 to 4,352 per cubic millimeter. These cells were observed first on the third day of treatment. Erythrophages appeared in the peripheral blood on the fourth day, numbering from 186 to 868 per cubic millimeter, and were not found after the sixth day. Significance could not be attached to the results in the differential counts except that the mononuclear cells increased, in most instances,

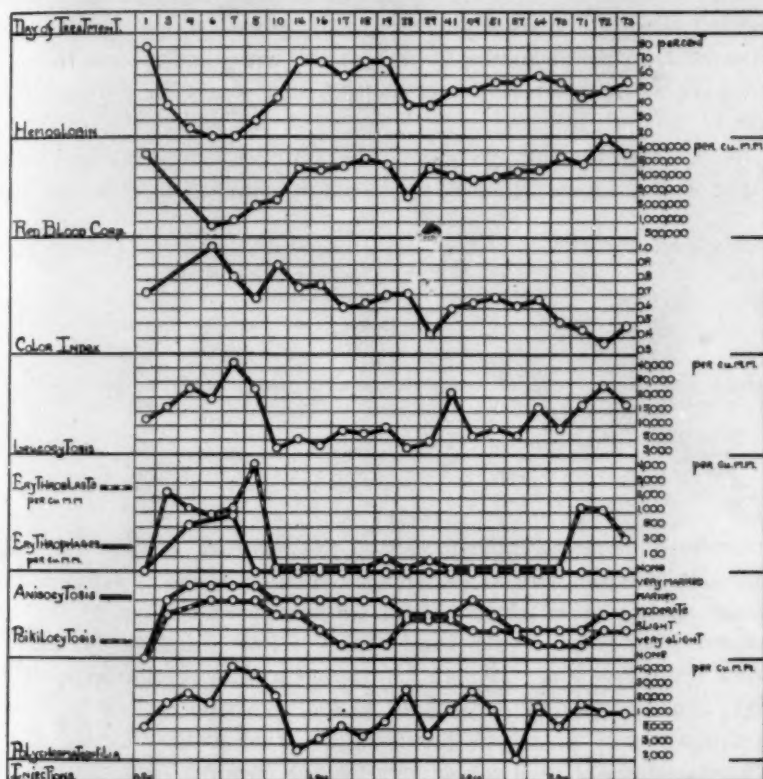


Fig. 1.—Severe anemia produced in rabbit no. 19 by injection of whole broth culture of a strain of (group I) *Cl. welchii*.

considerably above the normal. Simpson¹⁷ has shown that such counts are subject to wide variation in rabbits and that caution must be exercised in drawing conclusions from them. Eosinophilic leukocytes always remained below 1 per cent and have, therefore, not been tabulated separately, but have been included under polymorphonuclear leukocytes.

At the height of the intoxication, the rabbits became lethargic but did not manifest any convulsive movements. The loss of body weight ranged from 1 to 25 per cent.

In the most severe poisonings by whole culture, the blood of the animal showed a spontaneous macroscopic agglutination of the red corpuscles from the third to the sixth day. When the washed cells of the animal were mixed with normal rabbit serum, agglutination occurred at once, but the serum of the experimental animal failed to agglutinate the erythrocytes of normal rabbits. It is evident, therefore, that the clumping depended on a change in the cells rather than alteration of the plasma. The serum is necessary for agglutination, however, since the washed cells failed to clump in salt solution or in citrate solution used as controls. This phenomenon of agglutination was also observed in the rabbits injected with toxic bacteria-free filtrates, but to a less extent. This behavior of the erythrocytes of rabbit 24 is indicated in table 1.

In the animals just discussed, the intoxications were not lethal. Larger doses, however, such as 5 cc. of potent bacteria-free toxic

TABLE 1 (Rabbit 24).—Agglutination of Erythrocytes in Blood During Acute Intoxication with Whole Culture of *Cl. Welchii*

Washed Erythrocytes of Rabbit	Rabbit Serum			Citrate Solution, 2.5 per Cent	Salt Solution, 0.9 per Cent
	Normal		Toxic 24		
	1	2			
24 toxic.....	++++	++++	++++	0	0
1 normal.....	0	0	0	0	0
2 normal.....	0	0	0	0	0

filtrate, injected intravenously, caused the death of a rabbit weighing 2,500 Gm. in from two to six hours. In such animals, marked spontaneous agglutination of red blood corpuscles was observed in blood obtained from the ear vein during life. After death the evidence of violent hemolysis was striking; abundant capillary hemorrhages in the lungs; thin Burgundy-colored fluid in the pericardium; laked blood in the cardiac ventricles; hemoglobin-tinged urine in the bladder, in one instance containing 1.6 Gm. hemoglobin per hundred cubic centimeters, and tremendous engorgement of the abdominal organs and the large vessels of the abdomen.

CHRONIC DISTURBANCES

Strains of *Cl. welchii* of groups 1 and 2 administered to rabbits in repeated small intramuscular injections of whole cultures and of toxic filtrates induced a chronic intoxication with anemia. At first a dose of 0.1 cc. of whole culture was given, and the dose was repeated at irregular intervals and gradually increased over a period of several months. After a time, the animals were able to tolerate much larger doses without an appreciable lowering of the hemoglobin or erythrocyte

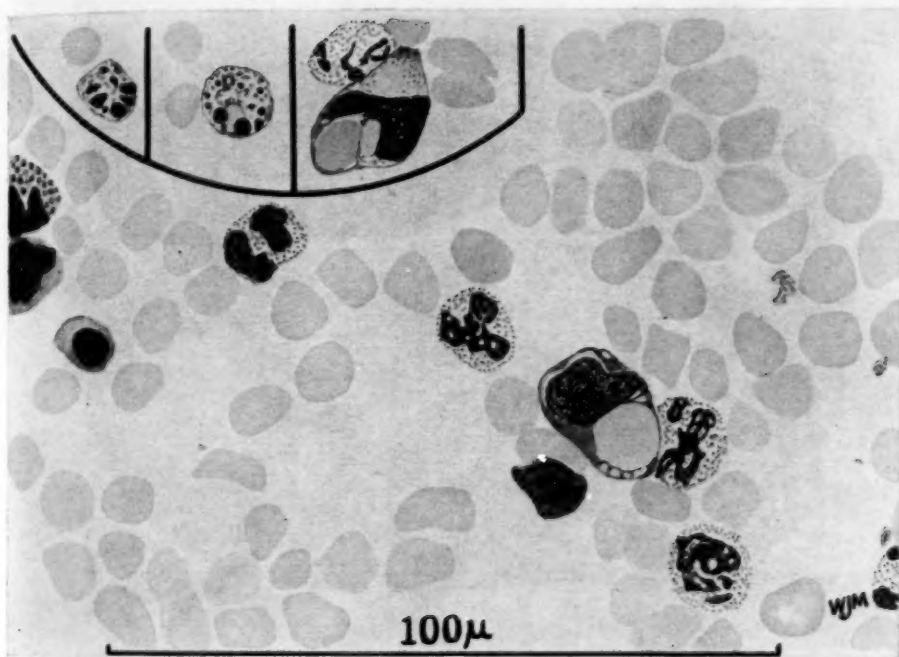
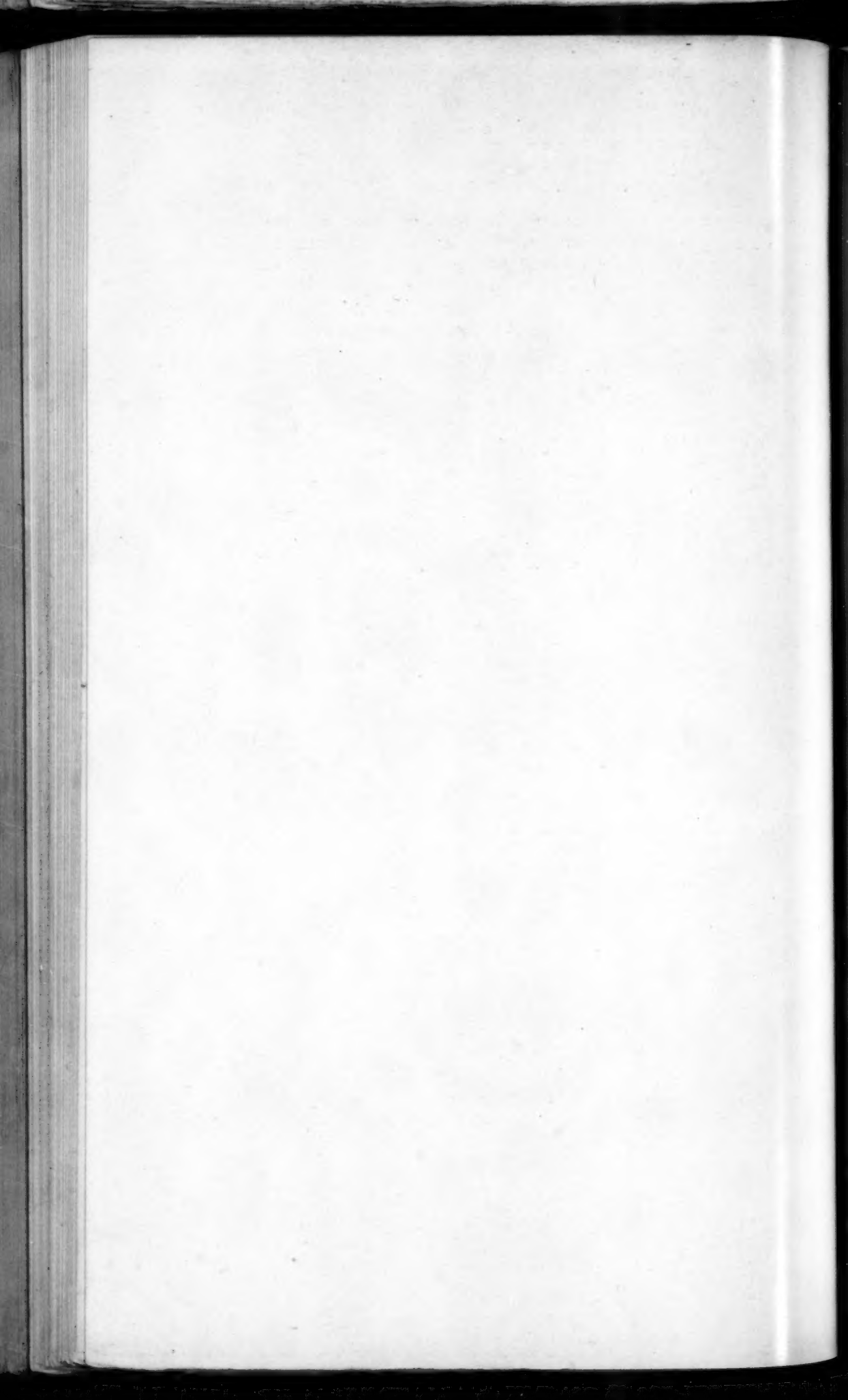


Fig. 2.—Blood smear from rabbit no. 19 illustrating severe toxic anemia on the seventh day of treatment. Anisocytosis and polychromatophilia are marked. An erythroblast may be seen at the left. A clasmatocyte with ingested macrocytic red cell can be observed in the field to the right of the center. Another clasmatocyte pictured in the right hand insert, drawn from another field in the same blood film, exemplifies erythrophagocytosis of three red blood cells of varying size and hemoglobin content. The cells containing nuclear fragments, pictured in the two inserts to the upper left corner of the drawing, are types frequently found in these severe experimental anemias and probably result from the toxic processes induced. The length of the line represents 100 microns. The colored drawing was made by Dr. Ward J. MacNeal.



count, so that intravenous injections of 5, or even 10 cc., were given at from two to four-day intervals toward the end of an experiment.

The blood changes in these animals were less violent. In the rabbits receiving whole culture the lowest observation of hemoglobin was 30 per cent, or 4.11 Gm. per hundred cubic centimeter in rabbit 25, and the lowest erythrocyte count was 1,280,000 per cubic millimeter. The color index tended to rise but remained below 1 except in one animal with hemoglobinemia, in which it rose to 2.08. It will be recalled that the normal average color index for these rabbits was 0.63. The leukocyte counts varied from 5,400 to 46,200 per cubic millimeter, except

TABLE 2.—*Protocols of Acute Disturbances in Rabbits*

Day of treatment.....	Rabbit 32 Injected with Whole Culture of Cl. welchii, Group 1					Rabbit 75 Injected with Toxice Filtrate of Cl. welchii, Group 1				
	Normal 1	3	4	5	7	Normal 1	3	4	5	
Dose of culture.....	0.3	None	None	0.2	Killed	2.0	None	2.0	Killed	
Per cent of hemoglobin...	75	60	48	38	20	90	37	36	25	
Red cells ($\times 1000$).....	6060	4160	2540	1400	700	5860	2800	2040	1800	
Color index.....	0.62	0.73	0.92	1.35	1.42	0.77	0.66	0.90	0.69	
White blood cells.....	6000	12000	15200	17000	20000	9400	41000	44400	46000	
Differential count										
Polymorphonuclears...	19	8	21	11	28	18	40	24	51	
Large lymphocytes.....	13	9	1	0	0	17	2	5	1	
Small lymphocytes.....	27	34	52	48	53	39	22	33	24	
Monocytes.....	38	44	21	29	18	16	9	15	11	
Clasmatocyte type.....	0	0	0	0	0	5	25†	13	9	
Basophils.....	3	5	5	12	1	5	2	9	4	
Erythroblasts*.....	0	5	1	17	9	0	0	0	0	
Erythrophages*.....	0	0	0	0	0	0	0	1	0	
Anisocytosis.....	—	++	+++	+++	+++	—	+	++	+++	
Poikilocytosis.....	—	+	+	++	++	—	+	+	+	
Polychromatophilia.....	30	90	100	220	220	0	60	70	110	
Crenation.....	—	—	+	+	±	—	—	—	—	
Agglutination of red blood cells.....	—	±	+	+++	+++	—	—	—	—	
Grams body weight.....	2379	2340	2310	2372	2500	2434	2124	2000	1903	

* Number per hundred leukocytes counted.

† Vacuolated and containing phagocytosed debris.

for a terminal leukopenia of 2,800 in rabbit 11. Anisocytosis, poikilocytosis and polychromatophilia were marked between the third and the twentieth day, but were observed, as a rule, in slight degree only at later periods. Erythrophagocytosis in the peripheral blood was observed in one animal, ninety-six erythrophages per cubic millimeter of blood being found. The advent of these cells in the peripheral blood of the rabbit would appear to depend on a severe and abrupt disturbance. Nucleated red cells were found in numbers varying from 62 to 3,136 per cubic millimeter. In general, the rabbits injected with repeated small doses of bacteria-free filtrates behaved in a similar manner, but the disturbances were somewhat less severe. In none of these animals was spontaneous agglutination of erythrocytes observed. The greatest final loss in weight was only 15 per cent, but varied with the toxicity of the

material injected. A striking feature of these experiments was the tolerance acquired by the rabbits such that repeated very large doses failed to cause appreciable destruction of the blood.

Strains of groups 3 and 4 were also employed, both being nontoxic but the former hemolytic in vitro. Rabbits treated over long periods with the hemolytic strains of group 3 showed a reduction of hemo-

TABLE 3 (Rabbit 9).—Specimen Protocol (Abridged†) of Chronic Infection in Rabbit Produced with Whole Broth Cultures of Group 1 Strain, *Cl. Welchii*

Day of treatment.....	Normal 1	3	5	7	16†	22†	29†
Dose of culture.....	0.1	0.1	None	None	0.1	0.2	0.3
Per cent hemoglobin.....	80	60	45	50	68	57	70
Red cells (×1000).....	7380	6380	3220	4540	4660	5220	4900
Color index.....	0.54	0.47	0.70	0.55	0.73	0.54	0.71
White blood cells.....	12000	29400	14800	9000	8200	10800	12600
Differential count							
Polymorphonuclears.....	52	53	61	57	44	70	37
Large lymphocytes.....	0	0	2	4	6	3	5
Small lymphocytes.....	14	18	20	22	24	17	22
Monocytes.....	30	24	16	12	23	8	33
Basophils.....	4	5	1	5	3	2	3
Erythroblasts*.....	0	0	1	0	0	0	0
Anisocytosis.....	—	++++	++++	++++	+	+	+
Poikilocytosis.....	—	+	+	+	++	+	+
Polychromatophilia*.....	7	47	100	400	50	50	50
Grams body weight.....	1903	1810	1810	1841	1810	1934	2081
Day of treatment.....	31	50†	64†	92†	94	96	99†
Dose of culture.....	0.4	3.0	iv 5.0	iv 6.0	iv 5.0	None	Killed
Per cent hemoglobin.....	68	60	55	70	73	75	55
Red cells (×1000).....	4440	5640	5200	4520	4540	5340	4500
Color index.....	0.77	0.53	0.52	0.77	0.81	0.70	0.61
White blood cells.....	8800	15200	17200	10000	22000	73000	19600
Differential count							
Polymorphonuclears.....	20	51	13	18	12	37	30
Large lymphocytes.....	2	8	6	4	12	0	1
Small lymphocytes.....	40	7	26	44	22	17	47
Monocytes.....	35	32	52	28	54	46	23
Basophils.....	2	2	3	6	0	0	0
Erythroblasts*.....	0	4	0	0	1	2	1
Anisocytosis.....	++	++	++	+	+	+	++
Poikilocytosis.....	+	+	++	+	+	+	+
Polychromatophilia*.....	30	350	50	200	100	50	50
Grams body weight.....	2081	1965	2248	2279	2000	1779

† Observations on blood on days 9, 11 and 14 omitted from table; no inoculation in this period; observation data on day 19 are omitted, no inoculation; observation data on days 24 and 26 omitted, 0.3 cc. culture given on each day; observation data on days 33, 40 and 43 omitted, a dose of 1.0 cc. was given on each of these days; data for days 52 and 58 omitted, no inoculation; data for day 68 omitted, no inoculation; data for day 98 omitted, no inoculation on this day; intravenous inoculation is indicated by iv preceding the dose.

* Number per hundred leukocytes counted.

globin to 6.85 Gm. per hundred cubic centimeter and of red cells to 3,000,000 per cubic millimeter. The maximum leukocyte count observed was 13,600 per cubic millimeter, not above the normal limit. Anisocytosis, poikilocytosis and polychromatophilia were marked from the seventh to the eleventh day but were less conspicuous afterward. Erythroblasts were observed, as many as 270 per cubic millimeter when the foregoing changes were most pronounced. Erythrophagocytosis was

not seen in the peripheral blood. The final loss of weight was 11.6 per cent. Curiously enough, the injection of the nontoxic, nonhemolytic strains of group 4 was followed by similar, but somewhat less pronounced, changes. It would seem that the anemia was due more to the bacterial substance than to the special hemolytic agent.

CONTROL ANIMALS

Rabbits injected with cultures of *Cl. bifermentans*, by the same technical procedure, also became anemic, the red cells being reduced to 3,360,000 per cubic millimeter and the hemoglobin to 6.85 Gm. per hundred cubic centimeters. In only one instance did the color index

TABLE 4 (Rabbit 45).—Abridged † Protocol of Rabbit Protected by Antitoxin Obtained from Rabbit Treated with Toxic Filtrate of *Cl. Welchii*, Group 1

Day of treatment.....	Normal 1	4	6	15†	22	30	43†
Dose of toxin*.....	1.0	2.0	2.0	None	None	None	Killed
Dose of antitoxin*.....	0.6	1.2	1.2	None	None	None	
Per cent hemoglobin.....	75	75	80	75	75	73	78
Red cells (×1000).....	6020	6460	8720	6500	6440	6320	5900
Color index.....	0.56	0.58	0.45	0.57	0.58	0.57	0.66
White blood cells.....	9800	9200	9600	15600	11800	16000	7600
Differential count.....							
Polymorphonuclears.....	28	36	14	24	17	28	35
Large lymphocytes.....	8	20	17	7	24	9	14
Small lymphocytes.....	20	8	15	45	30	44	31
Monocytes.....	40	26	57	16	24	18	11
Clasmatocyte type.....	0	8	17	3	5	4	5
Basophils.....	4	2	10	5	0	4	4
Erythroblasts*.....	0	0	1	0	0	0	0
Anisocytosis.....	—	—	±	±	±	±	±
Poikilocytosis.....	—	—	±	—	—	—	+
Polychromatophilia*.....	150	70	80	70	50	30	60
Grams body weight.....	2745	2779	2676	2465	2562	2686	2655

† Data of observations on day 8 are omitted from the table, no injection on this day; data on day 37 omitted, no injection on this day; animal finally killed on day 43.

* Rabbit 45 was treated with the antitoxin from rabbit 12. The mixture of toxin and antitoxin was allowed to stand two hours at room temperature and was then injected intravenously. Erythroblasts and polychromatophilic cells per hundred leukocytes counted.

reach 1. Moderate anisocytosis and slight poikilocytosis were observed. Erythroblasts reached 352 per cubic millimeter in one instance. Loss of weight was insignificant.

When cultures of *Cl. sporogenes* were employed in the same way, the rabbits behaved in different ways. In some the hemoglobin and erythrocytes tended to increase slightly; in others, they diminished. A microcytic anisocytosis with moderate polychromatophilia was present, but nucleated red cells were not seen. Loss of weight up to 12 per cent was observed.

A rabbit was also injected intravenously with sterile distilled water, as a hemolytic agent, in doses of from 2 to 4 cc. daily for nineteen days. Counts made thirty minutes after injection revealed a minimum of 2,644,000 red cells per cubic millimeter. Compensation was rapid,

for the lowest count observed just before injection (on the next day) was 3,220,000. Anisocytosis and polychromatophilia were moderate on the seventeenth day and erythroblasts appeared on the twelfth day numbering 124 per cubic millimeter. The loss of weight was 36 per cent.

Another rabbit was given intramuscular injections of butyric acid, a substance produced by *Cl. welchii*, 1 per cent solution in distilled

TABLE 5 (Rabbit 13).—Abridged † Protocol of Control Rabbit Injected with Whole Broth Culture of *Cl. Bifermentans*

Day of treatment.....	Normal 1	7†	21†	26	29	33	47†
Dose of culture.....	1.0	1.0	2.0	3.0	None	3.0	iv 4.0
Per cent hemoglobin.....	75	75	70	75	68	75	75
Red cells (×1000).....	6000	5800	6560	6020	4600	5780	6080
Color index.....	0.54	0.64	0.53	0.56	0.73	0.65	0.62
White blood cells.....	5000	5800	10200	8000	7000	6800	9000
Differential count							
Polymorphonuclears.....	32	6	28	22	12	35	16
Large lymphocytes.....	14	14	10	16	18	23	6
Small lymphocytes.....	16	35	46	32	32	13	66
Monocytes.....	35	44	15	30	36	22	10
Basophils.....	3	0	1	0	2	7	2
Erythroblasts*.....	0	0	0	0	0	0	0
Anisocytosis.....	—	++	+	+++	+++	++	±
Poikilocytosis.....	—	+++	±	++	++	±	±
Polychromatophilia*.....	40	20	50	450	200	80	30
Grams body weight.....	2624	2872	2686	2624	2810	2717	2717
Day of treatment.....	54	56	70†	72	75	77	86†
Dose of culture.....	iv 5.0	None	iv 8.0	None	iv 10.0	iv 10.0	Killed
Per cent hemoglobin.....	60	73	60	50	70	60	75
Red cells (×1000).....	4740	6180	5680	6720	5880	5230	6000
Color index.....	0.63	0.59	0.53	0.37	0.59	0.57	0.62
White blood cells.....	5000	7600	8400	7200	13000	8000	9400
Differential count							
Polymorphonuclears.....	4	20	24	14	18	16	17
Large lymphocytes.....	28	22	0	4	10	6	13
Small lymphocytes.....	24	34	28	46	37	48	26
Monocytes.....	42	24	46	36	35	23	44
Basophils.....	2	0	2	0	0	2	0
Erythroblasts*.....	0	0	0	0	0	0	0
Anisocytosis.....	+	+	++	++	++	+	+
Poikilocytosis.....	+	+	+	+	+	+	+
Polychromatophilia*.....	30	50	150	180	150	160	210
Grams body weight.....	2748	2965	3062	3124	3124	3062	3186

† Observation on blood on day 5 omitted from table, 1.0 cc. culture given on this day; observation data on days 12, 16 and 19 omitted from table, no inoculation on these days; data on day 68 omitted, no inoculation on this day; data on days 82 and 84 omitted, intravenous injection of 10 cc. on day 84; animal killed on day 86. Intravenous injection is indicated by iv preceding the dose.

* Number per hundred leukocytes counted.

water, seventeen injections of from 1 to 2 cc. over a period of forty-four days. The hemoglobin diminished to 5.46 Gm. per hundred cubic centimeters and the red cells to 2,760,000 per cubic millimeter. A marked microcytic anisocytosis and a moderately severe poikilocytosis were observed during the last twenty-two days. A few erythroblasts, 64 per cubic millimeter, appeared on the thirtieth day and 100 per cubic millimeter were observed on the fifty-second day. Loss of weight was 15 per cent.

These results suggest that many factors are probably concerned in the destruction of blood brought about by *Cl. welchii*. The butyric acid may play a part, but alone it does not give rise to the blood picture induced by injection of the bacterial culture. This indication is further supported by the observation that old toxins, which have lost their

TABLE 6 (Rabbit 14).—Abridged † Protocol of Control Rabbit Injected with Whole Broth Culture of *Cl. Sporogenes*

Day of treatment.....	Normal 1	3	8	12	15	17	22
Dose of culture.....	1.0	1.0	1.0	1.0	1.0	2.0	3.0
Per cent hemoglobin.....	70	70	75	73	73	55	70
Red cells (×1000).....	5000	4680	6140	5240	6520	5720	5840
Color index.....	0.70	0.76	0.61	0.70	0.56	0.48	0.60
White blood cells.....	7200	15200	10200	7400	9400	6600	17600
Differential count							
Polymorphonuclears.....	16	5	31	47	45	25	50
Large lymphocytes.....	37	22	8	5	27	16	8
Small lymphocytes.....	32	19	6	16	5	30	0
Monocytes.....	15	54	51	30	22	25	28
Basophils.....	0	0	4	2	1	4	4
Erythroblasts.....	0	0	0	0	0	0	0
Anisocytosis.....	—	+	+	++	+	+	+++
Poikilocytosis.....	—	+++	+	+	+	+	+
Polychromatophilia*.....	30	30	100	900	50	60	80
Grams body weight.....	2593	2717	2717	2655	2562	2562	2717
Day of treatment.....	29†	43†	50	52	64	68†	71
Dose of culture.....	3.0	iv 4.0	iv 5.0	None	None	None	Killed
Per cent hemoglobin.....	60	60	60	60	40	40	45
Red cells (×1000).....	4600	7160	6000	4740	4840	3820	2320
Color index.....	0.61	0.42	0.45	0.63	0.41	0.52	0.97
White blood cells.....	8200	11200	17200	9900	9000	7400	5400
Differential count							
Polymorphonuclears.....	33	30	28	28	20	12	4
Large lymphocytes.....	2	40	20	4	0	3	18
Small lymphocytes.....	28	12	20	14	30	29	20
Monocytes.....	36	14	28	52	38	50	50
Basophils.....	1	4	4	2	12	6	8
Erythroblasts.....	0	0	0	0	0	0	0
Anisocytosis.....	++	++	+	+	++	+++	+++
Poikilocytosis.....	+	+	+	+	+	+	+
Polychromatophilia*.....	80	30	30	100	500	300	220
Grams body weight.....	2500	2500	2500	2586	2186	—	2217

† Observation data of day 24 omitted from the table, no inoculation on this day; data of day 31 omitted, no inoculation on this day; data of day 66 omitted, no inoculation on this day. Intravenous inoculation is indicated by iv. Animal was killed on day 71.

* Number per hundred leukocytes counted.

toxic property but still retain their hemolytic property, as shown by tests in vitro, have also lost, in part, their ability to induce severe anemia.

IMMUNITY

As briefly reported in an earlier communication,¹⁹ the rabbits treated with products of *Cl. welchii* tend to acquire an immunity. In most instances the red cells returned to within 500,000 per cubic millimeter

19. Patterson, M. B., and Kast, Ludwig: Experimental Toxic Anemia Produced with *Bacillus Welchii*, Proc. N. Y. Path. Soc. **26**:17, 1926.

of the original count. This recovery during continuation of the intoxication presents a distinct contrast to the behavior in the chronic progressive fatal anemias of man and speaks against an etiologic relation of *Cl. welchii* to such anemias. After treatment for from twenty-five to fifty days the rabbits were able to withstand as much as 10 cc. of toxic filtrate or whole culture, an amount which would cause a fatal anemia in a new animal. Apparently there was no further increase in immunity after about the fifth week. When large injections of whole culture were given to such an immune rabbit, destruction of the blood did not occur, but nevertheless the animal became weak, ceased to eat and lost weight. In some instances, subcutaneous abscesses developed. Apparently an immunity sufficient to protect against the destruction of the blood failed to give complete protection against other untoward effects.

The serum of these immune rabbits was found to be protective against the toxin when introduced into normal rabbits or into pigeons. Thus it was found that 0.5 cc. of toxic filtrate mixed with 0.3 cc. of serum of immune rabbit no. 12 injected into the breast muscle of a pigeon did not have any evident effect. Rabbits were injected intravenously with toxic filtrate and immune serum mixed in equal amounts two hours before injection, the gradually increasing doses being given at intervals of two to three days until the control rabbits, receiving identical toxin without serum, had acquired a severe anemia. Inoculations were then discontinued, and the animals were kept under observation with frequent blood counts for an additional six weeks. Serum of rabbits immunized by toxin of group 1 strains gave complete protection, but the rabbits treated with toxin of group 2 strains yielded serum only partially protective against destruction of the blood.

Precipitin Reactions.—Specific precipitation was demonstrated by use of immune serum of rabbits treated with toxin of strains of groups 1 (rabbits 12 and 21) and 2 (rabbits 20 and 17), but not in those treated with filtrates of groups 3 (rabbit 10) and 4 (nontoxic). A rabbit treated with culture filtrate of *Cl. sporogenes* (rabbit 14) also gave positive specific precipitation with the homologous filtrate.

Agglutination.—Attempts to demonstrate agglutinins in the serum of these experimental rabbits, as well as in the blood of patients from whom virulent strains of *Cl. welchii* were obtained have, so far, given only negative results.

COMMENT

The severe anemia in rabbits produced in a few days by cultures of *Cl. welchii* was generally associated with leukocytosis, increased color index and the presence of degenerate red and white corpuscles and of phagocyted red corpuscles in the circulating blood. Erythrophagocytosis in the peripheral blood is probably a result of exaggerated activity of

clasmatoocytes in the ingestion of injured red cells. Doan and Sabin²⁰ have shown that increased destruction of red cells leads to excessive phagocytosis of this kind. The enormously increased erythrophagocytosis in the spleen resembles that observed by Voegtlin, Hooper and Johnson²¹ in trinitrotoluene poisoning in dogs. The acute destruction of the blood in our experimental rabbits may be regarded as analogous to acute toxic anemia of man. It would seem that *Cl. welchii* should receive consideration in relation to febrile anemia²² and especially in the types of anemia in children which are characterized by marked morphologic alterations of the blood.

The animals under prolonged treatment presented an increased tolerance to the products of *Cl. welchii* and their serum became antitoxic against this organism. One hesitates, therefore, to ascribe etiologic significance to *Cl. welchii* in pernicious anemia or in the other chronic forms of anemia in man. It is reasonable to suppose that the human body acquires immunity to its intestinal *Cl. welchii*, and it would, in that case, be necessary to assume the existence of other factors, still obscure, which contribute to the breaking down of this immunity in order to permit the products of this microbe to become effective.

PROTOCOLS

Of the ninety-two rabbits used in this study, the abridged protocols of six are presented in the tables. These are not entirely representative, but they serve as examples. In each instance the recorded examination of the blood was made preceding inoculation on the same date.

CONCLUSIONS

1. A severe toxic anemia can be produced in rabbits by one or two injections of whole culture or of toxic filtrate of *Cl. welchii*.
2. A secondary anemia can be produced by repeated injections of small doses of similar material.
3. Rabbits treated with repeated injections of the culture products of *Cl. welchii* over a period of several weeks acquire such immunity to the bacterial poison that they tolerate large subsequent inoculations.

20. Doan, Charles A., and Sabin, Florence R.: Normal and Pathological Fragmentation of Red Blood Cells; the Phagocytosis of These Fragments by Desquamated Endothelial Cells of the Blood Stream; the Correlation of the Peroxidase Reaction with Phagocytosis in Mononuclear Cells, *J. Exper. Med.* **43**:839, 1926.

21. Voegtlin, Carl; Hooper, C. W., and Johnson, J. M.: Hygienic Laboratory Bulletin, no. 126, 1920.

22. Brill, I. C.: Acute Febrile Anemia, *Arch. Int. Med.* **26**:244 (Feb. 26) 1926.

4. Serum of these immune animals serves to protect new animals against the bacterial poison, but such a serum is of high titer only when toxic strains of *Cl. welchii* have been employed in the immunization.

5. Specific precipitation is obtained by mixing fresh toxin with immune serum.

6. Strains of *Cl. welchii* which are both toxic and hemolytic are required for the production of severe anemia in rabbits. Hemolytic nontoxic strains cause only slight anemia.

7. In these experiments it has been impossible to produce in rabbits a chronic fatal megaloblastic anemia comparable to pernicious anemia in man.

Laboratory Methods and Technical Notes

MICROPRECIPITATION TEST FOR SYPHILIS*

M. G. PETERMAN, M.D., MILWAUKEE

In the examination of infants and children, it is often difficult to obtain more than small amounts of blood. Venipuncture is sometimes trying, and it is better to avoid it, if possible. Puncture of a longitudinal sinus is a hazardous procedure except for the physician who is familiar with the technic. A careful examination is not complete without a diagnostic test for syphilis. The Wassermann test is often omitted because of the difficulty in obtaining blood. The complement-fixation test or any of its modifications involve time-consuming complexity and difficulties in standardization. The Wassermann test is an indirect, empiric procedure requiring five different animal reagents for its completion, i. e., human serum (antibody), guinea-pig serum (complement), rabbit serum (amboceptor), beef heart serum (antigen) and the serum made from the red corpuscles of sheep.

A microprecipitation test has been described based on the test described by Kline and Young,¹ which requires only 0.05 cc., or even 0.025 cc. (one-half drop) of serum.² This small amount of blood may be obtained easily by puncture through the skin and aspiration with a capillary tube. Similar amounts of spinal fluid may also be tested.

In addition to the small amounts of blood or spinal fluid required, this test has the advantage of simplicity—a minimum of equipment, one reagent (antigen), and a relatively short time for completion. This test, like the Kahn reaction, has a scientific basis and may be used quantitatively as a chemical reaction. The equipment consists of a pipet graduated in 0.001 cc., a hanging drop slide, a glass slide and a thermometer. The antigen, which is prepared according to the method of Neymann and Gager,² may be purchased directly from the Michigan State Board of Health, Lansing (Kahn's antigen). This antigen is diluted with physiologic sodium chloride solution, according to its titer, and is ready for use. The measured amount of the solution should be poured directly into the measured amount of antigen and the two mixed by pouring back and forth several times. The serum or spinal fluid is inactivated at 56 C. for thirty minutes. Then 0.05 cc. or less is placed into the concavity and 0.01 cc. of diluted antigen or one fifth the amount of serum is added, and the mixture is rotated. The slide is allowed to stand at room temperature or in an incubator at 38 C. for ten minutes. The slide is again rotated and the result read under the low power microscope. The precipitation is graded according to the amount, +, ++, +++ or ++++.

In a previous paper³ the results of 1,109 tests on serums and spinal fluid have been reported. The microprecipitation test was in accordance with the clinical diagnosis in 98.9 per cent of the 500 cases, while the Wassermann test was in accordance in 92.2 per cent. One thousand tests have now been completed. A 5 to 1 dilution of serum antigen was used in the last 500 tests. Spinal fluid is used in the same amounts as serum. In this series, whenever

* From the Milwaukee Children's Hospital.

1. Kline, B. S., and Young, A. W.: Microscopic Slide Precipitation Test for Syphilis: Preliminary Report, J. A. M. A. **86**:928 (March 27) 1926.

2. Peterman, M. G.: Microprecipitation Test for Syphilis, Am. J. Dis. Child. **34**:404 (Sept.) 1927.

there was a relative or absolute disagreement between the Wassermann and microprecipitation tests, a specimen of the serum or spinal fluid was sent to Dr. W. F. Lorenz, Director of the Wisconsin Psychiatric Institute, for verification. The technic used in checking our results was a system based on varying amounts of complement. In one control tube, no complement is added; in the next two tubes, 1 unit of complement is added, and in one of these tubes, antigen is used. The third and fourth series of two tubes each contain 2 and 3 units of complement following the same arrangement of a control tube and an antigen tube. The serum is used in amounts of 0.03 cc. with the sheep hemolytic system and 10 units of acetone insoluble antigen.

The results of the first 500 tests have been reported in detail.² In the last 500 tests there was agreement between the microprecipitation test and the Wassermann test (Noguchi) in 417 cases, 83.4 per cent. Both tests were negative in 376 cases and both positive in 41. There were seventy-three positive microprecipitation tests with negative Wassermann reactions. Thirty-three per cent of these specimens were sent to the Wisconsin Psychiatric Institute; thirty-one were reported negative and two were reported ++.

The seventy-three positive microprecipitation tests with negative Wassermann reactions were obtained from thirty-eight persons with congenital syphilis; from the spinal fluid of one person with congenital syphilis; from three mothers and four fathers of children with congenital syphilis and from seven brothers and eight sisters of persons with congenital syphilis. In twelve + precipitations there was no clinical evidence of syphilis.

There were six positive Wassermann reactions with negative precipitation tests. One ++++ Wassermann reaction was obtained in the serum of a person with congenital syphilis, two ++ Wassermann reactions in a mother and father of a child with congenital syphilis, one + Wassermann reaction in a person with congenital syphilis after extensive treatment; one ++ and one + Wassermann reaction in two children without clinical evidence of syphilis.

Three serums with ++++ precipitations and ++ Wassermann reactions were noted in cases of congenital syphilis in which treatment was being given. One ++++ Wassermann test with a ++ precipitation test was obtained from a syphilitic mother who was under treatment.

In the 1,000 microprecipitation tests that were checked with Wassermann tests there was agreement in the two tests in 87.25 per cent. The microprecipitation test was in accordance with the clinical diagnosis in 96.5 per cent; the Wassermann test, in 87.2 per cent.

Eight hundred and thirty-three microprecipitation tests with Wassermann controls (Wisconsin Psychiatric Institute) have been made under the direction of Dr. T. L. Squier in the Department of Preventive Medicine of the A. O. Smith Corporation. In these cases (all adults), the Wassermann reaction accorded with the clinical observations in 98.1 per cent and the microprecipitation test in 99.7 per cent.

COMMENT

A microprecipitation test has been described which requires only one-half drop of serum or spinal fluid. The test is simple, requiring a minimum of apparatus and a short time for its completion. The test has been found to be in accordance with the clinical observations in 96.5 per cent of the cases, while the Wassermann test has been in accordance with such observations in 87.25 per cent. In adults, the variation between the two tests has not been so great. The greater accuracy of the precipitation test seems to be in con-

genital syphilis; fifty-four persons with congenital syphilis gave positive precipitations and negative Wassermann reactions. In the treatment of children with congenital syphilis, it is found that the precipitation test is the last to become negative and when treatment is prematurely discontinued, the first to become positive.

167 Seventeenth Street.

A MODIFICATION OF THE PEROXIDASE REACTION WITH SODIUM NITROPRUSSIDE AND BENZIDINE *

MAX M. STRUMIA, M.D., PHILADELPHIA

In a series of studies on the blood morphology in cases of acute leukemia, a number of methods were tried for staining the oxidase granules of myelogenous cells. Among these, the method proposed by Goodpasture¹ proved to be the most satisfactory, because of its simplicity and dependability.

This method, however, has two disadvantages. The first is the fact that the mixture deteriorates in a few weeks, so that it is necessary to weigh the chemicals each time the solution is made. The second is that fuchsin is an unsatisfactory cellular stain, not giving clear cell pictures and interfering with subsequent staining by other dyes.

These disadvantages are overcome by the following modification of Goodpasture's technic. Two stock solutions are prepared:

Solution A: Sodium nitroprusside, 5 per cent aqueous solution.

Solution B: Benzidine, 2.5 per cent alcoholic solution.

For use, mix 1 cc. of solution A and 95 cc. of 95 per cent alcohol; add 2 cc. of solution B and 2 cc. of fresh solution of hydrogen peroxide.

This solution must be allowed to ripen for an hour or more to give the best results. While this mixture keeps at least as well as the original Goodpasture solution, the stock solutions A and B keep indefinitely; the mixture can easily be prepared each time it is needed by mixing the stock solutions in proper proportion.

The technic of staining is the same as in the original Goodpasture method. The dried blood smear (which should be fresh) is covered with the solution for one or two minutes. An equal amount of distilled water is then added, and the preparation is stained for from three to five minutes until, under the low power of the microscope, blue granules appear in the polymorphonuclears and large mononuclears. The slide is then washed in running water for about fifteen minutes.

The second modification is a substitution of any of the Romanowski stains for fuchsin. Giemsa stain (1 part of the solution to 20 of distilled water for fifteen minutes) is excellent, but for optimal results this should be preceded by May-Grünwald stain, diluted with an equal amount of neutral distilled water and allowed to act for two minutes.

By this method, excellent differentiation of the cells is obtained. Oxidase granules are not affected by the procedure and are easily recognized.

The same method can be applied to frozen sections of tissues fixed in formaldehyde.

*From the Laboratory of Pathology, School of Medicine, University of Pennsylvania.

1. Goodpasture, N. W.: J. Lab. & Clin. Med. 4:442, 1919.

General Review

PATHOLOGIC ANATOMY OF INFLUENZA

A REVIEW BASED CHIEFLY ON GERMAN SOURCES

FRANZ LUCKSCH, M.D.

Professor of Pathologic Anatomy in the German University in Prague
PRAGUE, CZECHOSLOVAKIA

A number of years have gone by since the last important epidemic of influenza, which swept over the whole inhabited world toward the end of the great war. The time which has passed and the perspective in which that event can now be viewed should allow a fairly unprejudiced consideration of the circumstances. It seems, therefore, not unfitting to attempt to determine whether the last epidemic produced anything new in pathologic anatomy. An answer to this question implies a comparison with the facts obtained in former epidemics. Although I shall discuss chiefly the anatomic observations, the question of the etiology of influenza cannot be passed over; today every investigation in pathologic anatomy includes an investigation of the etiology. Nor shall I limit this study to the etiology of influenza itself; I shall include all diseases that appear as sequelae to it or that can be or have been brought into relationship with it. Finally, I shall consider whether the pathologic anatomist is in a position to diagnose influenza from his own observations alone, or whether he should consult specialists in more or less distantly related diseases. It is evident that it will be impossible to confine attention to pathologic anatomy; various aspects of the disease, especially the clinical, will claim a share.

It is not easy to institute a comparison between the pathologic-anatomic changes as they were determined in the last epidemic and as they were observed in earlier years, for the reason that a comprehensive treatment of the material, such as is given by Kuczynski and Wolff, in Lubarsch-Ostertag's "Ergebnisse," is not in existence for the earlier epidemics. Former treatises on the subject, particularly those on the previous great epidemic from 1889 to 1892, were written either by clinicians or by bacteriologists. Leyden and Guttman's work, in which the chapter on pathologic anatomy was prepared by Ribbert, is an exception. Furthermore, it is clear that in certain respects a comparison is impossible, since in the intervening years notable advances have been made in pathologic-anatomic technic; I need refer only to descriptions of changes in the suprarenal glands, organs which used to be entirely disregarded at dissection. The impossibility of a comparison

will be especially evident in respect to the organs of internal secretion; in the older literature will be found only scant references to the nasal cavity and its accessory sinuses, which are of such importance in the spread of influenza both within and outside of the body.

ETIOLOGY

In studying the question whether the observations on influenza during the epidemic of the World War have changed materially the conceptions of the etiology of the disease, it may be recalled that before bacteriologic researches came to be employed, climatic conditions were considered the chief, if not the exclusive, factor in the causation of influenza. The first cold days in the fall, which commonly coincided with the first appearance of an epidemic, were especially incriminated; hence the term "*influenza di freddo*" (influence of the cold), which was at first applied to the disease.

In 1889, when influenza spread from Asia to Europe and to all the countries of the world, bacteriologic researches were instituted to determine the causal factor of the disease. Various organisms were considered, in turn, as the exciting agent. Some of these had been known previously, for example, the cocci. An important rôle was attributed at once to the pneumococcus. Some of the incriminated organisms, however, were newly detected, as, for instance, the flagellates, which were found by Klebs in the blood of patients with influenza. Kirchner discovered the organism regarded later as the influenza bacillus. However, the bacillus present in the cultures differed from that seen later under the microscope. Positive results were not obtained from researches carried out during the epidemics of 1889, 1890 and 1891. In 1892, Pfeiffer contended that he and his co-workers, Beck and Kitasato, had found a bacillus in the sputum of patients with influenza that had never been detected in sputum of patients with other diseases. Later, Pfeiffer obtained cultures of Kirchner's bacillus by using blood agar as a medium; other mediums gave negative results. He found the supposed influenza bacillus in respiratory secretions of patients with influenza; it was discovered also in pus from the ear of a patient with suppurative otitis media. The bacillus was not present in the blood, although a few were found in the spleen and in the kidneys. A bacillus described by Kitasato, Canon, Brushettini and Pfuhl proved to be nonspecific for the disease; on the other hand, Pfeiffer's results were confirmed by Weichselbaum, Huber, Chiari, Neisser, Bäumlér, Borchard, Pribram and others, and later became generally recognized. In 1893, Wassermann said, "Where there are influenza bacilli, there is influenza." In this contention he was supported by Ruhemann and later by Kruse (1894).

During the years immediately following, a similar bacillus was isolated in children with measles, scarlet fever, diphtheria, chicken-pox and whooping cough; also in tuberculous adults. This indi-

cated, it was alleged, that influenza may be accompanied by other infectious diseases, but did not detract from the etiologic rôle of the Pfeiffer bacillus. Evidently the influenza bacillus, like other pathogenic bacteria, might be the primary factor in combined infections or appear as a saprophyte in patients with bronchiectasis or with emphysema (Ortner's chronic nonfebrile influenzal bronchitis). Klieneberger found the influenza bacillus in 50 per cent of persons with coughs after the subsidence of the epidemic. Healthy carriers of influenza bacilli were found, during epidemic periods, as has been observed in other infectious diseases. In endemic cases of influenza (Leichtenstern) which occurred after an extensive epidemic, the bacilli were less numerous (Wassermann in 1900, Ruhemann, Park and Tedesco). At the same time, Saquepée, Besançon and de Jong contended that the influenza bacillus was not the exciting organism of the disease. Jochmann stated in 1909 that the bacillus in question is not positively specific for influenza in the sense that the gonococcus is for gonorrhea. On the other hand, Beck and Scheller asserted that the bacillus was specific. In 1914, Hübschmann reported three cases of pulmonary disease and one case of meningitis in which he asserted that influenza bacillus was the responsible factor. Kruse, on the other hand, declared that he had not found the bacillus in all cases of influenza observed by him during the past twenty-five years. In his opinion, influenza might be caused by an invisible organism, the so-called aphanozoon, which he had previously regarded as the causal factor of coryza. Selter expressed the opinion that the presence of the influenza bacillus has little or no significance in influenza.

Thus, Pfeiffer's theory of the rôle of the influenza bacillus in the etiology of influenza aroused controversy. During the epidemic of the so-called Spanish influenza, toward the close of the war, some investigators discovered the presence of a large number of influenza bacilli in the cases observed, while others did not discover any. Lucksch made an extensive study of the subject during the influenza epidemic of 1918. His bacteriologic examinations revealed the presence of the bacillus in the bronchioles, and he cultivated it on Voges agar. The results were confirmed by Pribram in Vienna. Ghon found the bacillus in 50 per cent of necropsies on patients who died from influenza. Levinthal cited analogous results by Gotschlich, Becher and Schürmann; also by Dietrich, Riemer and Levinthal in Budapest, and by Simmonds, Fränkel and Marchand and Herzog. Negative results were reported by von Gruber, Friedemann, Kolle, Mandlbaum, Schott-Müller (Benda, Schmorl and Lubarsch). Positive results were recorded in Spain, Italy, Denmark, Argentina and the United States, and especially in England, South Africa, the Netherlands and France. A few Frenchmen reported negative results. As in the epidemic of 1890, Lubarsch and Friedberger did not find the influenza bacillus until toward the end of the epidemic.

Among other organisms regarded as causative factors of influenza was a small diplostreptococcus. Some investigators pointed to filtrable organisms (von Angerer and von Leschke's *Microzoon influenzae*, and von Binder and Prell's, *Aenigmoplasma influenzae*. Identical or similar organisms were described by de Seixas Palma, Wade and Manalaing, by Pöppelmann, Kronberger, Olitzky and Gates, and by Rose Bradford, Bashford and Wilson. The etiologic importance of these organisms was later denied. Among others, Levinthal admitted that the influenza bacilli may have undergone a granular transformation in the body. Kruse held that influenza is caused by a filtrable virus. Friedberger advanced the view that a certain noxa facilitates the penetration of the influenza bacillus into the human body.

Search for a hypothetic invisible and filtrable virus was made, not only by means of the microscope and cultures, but also by experiments on man and animals. Experiments were made with filtrates of sputum, of nasal mucus and of liquids used for irrigation of the nose and throat, and with extracts of lung tissue. Researches on man were conducted by Selter, Kruse, Friedberger and Konitzer, da Cunha, Yamanouchi, Sakakami and Iwashima. Researches on man and monkeys were made by Lister and Taylor, Wahl, White and Lyall, Charles Nicolle and Lebailly. Fildes and McIntosh, also Fejes, experimented on monkeys; Gibson, Bowman and Connor on monkeys, rabbits and guinea-pigs. Moreschi, Micheli, Satta, Yamanouchi and Dujarric de la Rivière used blood filtrates in experiments on man. Finally, Gibson and his co-workers experimented with blood filtrates on monkeys, rabbits and guinea-pigs. Positive results with secretory products were obtained by Selter (?), Yamanouchi and other Japanese; by Nicolle and Lebailly, and by Gibson and his co-workers. Others reported doubtful or negative results. Positive results from experiments with blood filtrates were reported by Dujarric, and uncertain results by Gibson. Results of other investigations were negative. Evidently the results were discordant.

The results of experimental infection with the influenza bacillus were negative in man up to 1921. In that year Bieling and his co-workers discovered an immunity reaction to the bacillus in patients with influenza. The results were not unanimous. In the further course of the influenza epidemic, certain investigators found positive agglutination and deviation of complement by the blood serums of patients with influenza. Others maintained that the reactions were negative. Some reported positive results from preventive vaccination, especially with mixed vaccines. Wollstein, Seeligmann and Wolff denied the etiologic rôle of the bacillus on the basis of biologic study of immunity; others, including Levinthal, asserted that serologic reactions confirmed the etiologic significance of the bacillus. Levinthal and Kuczynski-Wolff stated in 1921 that their researches, extending over a period of three

years, tended to prove the etiologic rôle of the bacillus. Further experiments by Olitzky and Gates demonstrated the presence of a filtrable virus in influenza. Anaerobic cultures of this virus, injected into rabbits, induced symptoms similar to those of influenza in man, and the appearance of specific antibodies in the serum. The micro-organism was called *Bacterium pneumosintes*.¹ Blake and Cecil induced influenza in monkeys by inoculating them with cultures of influenza bacilli; Cecil and Steffens, also W. H. Park and G. Cooper, obtained similar results in man. At that time, Levinthal had described four types of the influenza bacillus: (1) the essential type; (2) and (3) variations of the essential type and (4) bacillus X, permanent transformation of the essential type. The modified types appear as degenerate forms in the patient's body. They are found toward the end of some epidemics (Preuss). Levinthal cited the researches of Olitzky and Gates, emphasizing that these need to be verified in man. He pointed to the work of Blake and Cecil, and that of Cecil and Steffens. His conclusion was that, thus far, the influenza bacillus cannot be considered the primary factor in influenza. Other organisms may enhance the virulence of this bacillus and also cause the disease. In Hildegard Lemm's experiments, serologic reactions confirmed the existence of morphologic variations of the influenza bacillus, as described by Levinthal. Further, the researches of Olitzky and Gates showed that the serum of convalescents from influenza agglutinates slightly (in dilutions from 1:4 to 1:40) *Bacterium pneumosintes*. This observation was supported by Gordon, Ledingham and Lister; later by Dettweiler and Hodges, Nishiva and Nakajama and others. It was denied by McIntosh, W. B. Dible and Leishman. Olitzky and Gates affirmed that *Bacterium pneumosintes* is absent in an ordinary "cold."

In 1918, it was announced that Ishiwara obtained positive results in man from inoculation with filtrates of sputum from patients with influenza. The existence of the filtrable virus was admitted by some and denied by others. On the basis of bacteriologic and serologic study, Kristensen concluded that the lack of homogeneity which characterized the influenza bacilli constituted an argument against the specific rôle of the bacillus in influenza. Later, Pfeiffer himself announced that the serodiagnosis of influenza is not unequivocal. In that connection, he referred especially to the work of the American investigators. Lubinski found that the receptor apparatus in specimens of the bacillus varies. Pfeiffer and Hottinger noted that *Bacterium pneumosintes* resembles the influenza bacillus, but that the serologic properties of the two are

1. Greek, "destroyer of the lung." Olitzky and Gates believed that this organism injured the lung, thus favoring penetration of the influenza bacillus and of other bacteria, and enhancing their pathogenic action.

different. Pfeiffer's conclusion is as follows: "We must recognize that modern methods of bacteriologic study have been unable as yet to solve the influenza problem." Nevertheless, Pfeiffer was convinced that his claim of the etiologic rôle of the influenza bacillus conformed most closely to the results of the majority of research workers.

Passing in review all that has been said, it will be seen that, in spite of the amount of research conducted during the war epidemics, the etiology of influenza has not been clearly established. In order to harmonize, as far as possible, the many divergent opinions that have been presented, I feel that I cannot do better than to cite a statement that I made in connection with a survey of the filtrable viruses, in which I called attention to the conditions obtaining in spirochetosis and also to the views that have recently been expressed with regard to typhus, hog cholera, tuberculosis and typhoid:

It will be seen, therefore, that the theories that I formed with reference to the infective agents in spirochetel form may be extended to the bacillar causative agents. It is possible that, not only as regards infective agents that appear in spirochetel form, but also with reference to those that are known to us only in the bacillar form, in the future, two distinct forms must be recognized: a visible form (appearing in the cultures) and a filtrable form that is not visible by ordinary methods. Further researches will be required to show whether the filtrable types are merely fragments or stunted forms, whose origin is due to unfavorable environmental conditions, or whether they are the precursors of the later visible types.

I believe that these words are equally applicable to influenza, and that the conflicting views on the subject may thus be harmonized. The same opinion is expressed in Friedberger's last paper on invisible viruses. In the meantime, some continued to consider the influenza bacillus, and others the invisible virus, as the causal factor of influenza. Kruse held that the two are not different, but merely two forms of the same organism. In Pfeiffer's opinion, the granular forms described by Leschke and others are nuclear forms of the influenza bacillus. Thus can be explained, he said, the fact that the bacillus is not found in the beginning of an influenza epidemic, since only the invisible virus is present at the start. According to Friedberger, gradual disappearance of the bacillus after the epidemic coincides with the reappearance of the invisible virus. This agreed with the statement of Preuss and Levinthal that degenerate or stunted forms of the bacillus appear toward the end of the epidemic. Thus was explained the fact that bacilli are not detected in some cases of epidemic influenza, or "influenza nostras," which occur between two epidemics (Leichtenstern). Such cases constitute hiding places for the invisible virus until its virulence is enhanced by some still unknown influence, whereupon a new outbreak occurs. This explains why the results of research made simultaneously in various places may be positive in

one place and negative in another. In one place, the epidemic may be of longer standing, and consequently the bacillus is present, while in another place, in which the epidemic starts, there is only the invisible form of the bacillus. Comparison of serologic results in influenza with those in typhus and typhoid tends to conform the existence of a filtrable form of *B. influenzae*.

PATHOLOGIC ANATOMY

The knowledge of pathologic anatomy in influenza has been extended in recent years as a result of the high mortality during the last epidemic, and, in addition, as a consequence of the improved technic of dissection. During the epidemics that marked the last decade of the nineteenth century, the morbidity (in Europe, at least) was 50 per cent of the population. In the epidemic at the close of the war, this rate in some countries reached 80 per cent; some statistics in Germany showed even 100 per cent. During the latest epidemic, the mortality in Germany was 37 per 10,000 population; in 1890, the mortality ranged from 8 to 10 per 10,000 inhabitants. In India and in the Lapland region, the mortality was much higher. In Samoa the mortality among the natives was 80 per cent. In the United States, the mortality was especially high in Connecticut. The total number of victims throughout the world was about 20,000,000, three fourths of them being in eastern Asia. The age groups most affected by the epidemic of the war were different from those of previous epidemics. Leichtenstern gives it as his observation that, for the most part, only aged, debilitated and tuberculous persons were the victims in the epidemic of 1890. On the other hand, the strongest persons among the population—namely, those aged from 17 to 35—contracted the disease during the war epidemic.

A relation between sex and mortality could not be established, either in the previous epidemics or in the war epidemic. Pregnancy increased the morbidity. According to Lubinski's observations, neither occupation nor social position nor unfavorable living conditions appeared to influence the number of deaths. The anatomico-pathologic researches were more productive of results during the war epidemic, owing to the fact that the mortality was high among young persons, in whom the lesions are usually more pronounced.

Two kinds of changes are observed in influenza: inflammatory lesions, induced by the exciting organism, and degenerative lesions, caused by toxic products eliminated by the organisms. Acute inflammation may present a serous, mucous, hemorrhagic, suppurative or pseudomembranous form; chronic lesions present an exudate (lymphocytic) or a productive form. The hemorrhagic and the suppurative are the most characteristic acute forms. Thus, the influenza bacillus is a pyogenic organism, the same as the staphylococcus or the streptococcus. Inflammatory lesions appear first in the place of invasion of the

bacillus or in the respiratory tract. The lesions may be located in any part of the body. The degenerative lesions are located chiefly in the parenchymatous organs, including the heart, the blood vessels and the central nervous system. Respiratory, intestinal and nervous forms of influenza occur, depending on the prevailing location of the lesions in the organs.

I. RESPIRATORY FORM OF INFLUENZA

The respiratory form is the most important, since lesions appear most frequently in the respiratory tract; besides, it is admitted that influenza is transmitted by respiration. Contrary to the course of the disease in the intestinal and nervous forms, the lesions may remain confined to the respiratory tract. In fact, any part of the respiratory apparatus may be first involved in influenza, the lesions being limited to that part. However, spread of the lesions to the lungs is a characteristic feature of the disease.

LESIONS OF THE RESPIRATORY SYSTEM

Nose.—In the nose, various forms of acute inflammation are observed. The serous form is rare; the most frequent forms are the mucopurulent, suppurative or hemorrhagic, the last mentioned often being associated with other forms. Pseudomembranous or fibrinous forms are also described. The chronic lesions have been studied less.

Eyes.—Next in frequency to inflammation of the nose is that of the conjunctiva, which is of a serous or seropurulent nature. Inflammation of the conjunctiva, which is one of the most frequent symptoms of the disease, appears simultaneously with rhinitis. In the last epidemic, the eyes seem to have been involved with special frequency, particularly the interior of the eye. On the exterior part, edema of the lid and keratitis are the chief lesions. E. Fränkel found changes in the eyes in 25 per cent of his case of influenza. These consisted mainly of hemorrhages occurring in different parts of the interior of the eye. Inflammatory lesions were much rarer. Metastatic suppurations of the eye and of the orbit have occurred; the latter have not infrequently extended to the meninges or the brain.

In earlier years, likewise, the eyes were markedly involved in influenza. Leichtenstern describes conjunctivitis in 71 per cent of his cases. He saw edema of the lid also, but rarely keratitis or inflammation in the interior of the eye.

Sinuses.—Inflammation of the accessory sinuses of the nose develops later. Inflammation occurs most frequently in the sphenoidal sinus, in the other sinuses or the orbit it is more rare; it usually ends in suppuration. The hemorrhagic form is also observed alone or associated with the suppurative form. Empyema of the sinuses may be the

cause of suppurative inflammation of the meninges. The influenza bacillus and the filtrable virus were found in the nasal secretion. The former was associated with various cocci, chiefly with *Micrococcus catarrhalis*. In the sinuses, the influenza bacillus is frequently associated with the streptococcus.

Involvement of the nose and of the sinuses has long been considered a characteristic symptom of influenza. However, anatomicopathologic study of this involvement was not begun during the epidemics in the nineties, and Weichselbaum was the first to make such research. In the nose and in the sinuses he found lesions analogous to those already described as occurring in the respiratory tract. Ghon's researches from 1905 to 1908, resulted in the detection of the influenza bacillus among other organisms in the nose and in the sinuses.

Mouth.—The buccal mucosa in influenza appears intact or only slightly affected. Nevertheless, as in other febrile diseases, the tongue is coated. Lesions of the tongue specific for influenza have not been noted. A thymicolymphatic condition is frequently observed. Inflammation of the soft palate may result only in redness and swelling or in pseudomembranous and necrotic lesions. There may be also extravasation of blood, miliary eruptions, vesicles and small abscesses.

Tonsils.—Moloslavich has called attention to involvement of the tonsils; in most cases, they are red and enlarged. Various forms of tonsillitis are observed; the most frequent is the suppurative form with abscesses. It is a characteristic phenomenon in influenza. The influenza bacillus was detected on the surface or within the tonsils, where it is not associated with other microbes.

Pharynx.—Lesions analogous to those in the soft palate are present also in the pharynx. A large number of streptococci were found in the necrotic form, sometimes associated with the influenza bacillus. Later the filtrable virus was isolated in the pharynx. The condition of the pharynx may involve the esophagus. The changes in the mouth, palate and tonsils were studied from the clinical rather than from the anatomic standpoint. Clinicians have called attention to the aspect of the tongue in influenza; to the bright red of the tip and of the margins (Leichtenstern).

Ear.—Lesions in the nose and in the pharynx may spread to the ear. It was held that lesions of the ear are not of hematogenic origin. They are found chiefly in the middle ear, and are often catarrhal, but more frequently suppurative. One or both ears may be affected, with involvement of the tympanic membrane. Myringitis bullosa is a characteristic condition with influenza. It may be complicated by involvement of the labyrinth or of the mastoid process and may spread to the sinuses or to the central nervous system.

Bacteriologic examination in diseases of the ear revealed, as a rule, mixed infections with influenza bacilli and cocci. Yet, sterile effusions were also found (dead bacteria, toxins or invisible virus).

The pathologic conditions in the ear were well known in the former epidemics. Leichtenstern reports the frequency of these complications as 2 per cent. The conception of myringitis bullosa was originated by Schwabach in 1890. In that epidemic influenza bacilli were found alone, or as part of mixed infections. According to Körner, frequent suppurations of the ear are mentioned even in the Hippocratic works in the description of an epidemic which was influenza, in Körner's opinion.

Larynx.—If the larynx participates in the disease, all the various inflammatory changes may be found. They may be restricted to redness and swelling of the mucous membrane; occasionally the edema may predominate; small spots or hemorrhages of various sizes may occur, but especially pseudomembranous changes. These may be caused either by influenza alone or by its combination with diphtheria, or by the latter alone following influenza. Influenzal croup may cause stenosis, just as the purely diphtheric form does. Ulcers have been described in the larynx, especially by Marchand, who points to their great similarity to ulcers that occur during typhoid. Deeper phlegmons and perichondritic abscesses occur occasionally. The contents of the larynx are variously described sometimes as bloody foam, sometimes as white foam and sometimes as thin pus.

Finally, it should be pointed out that neuritis of the inferior laryngeal nerve may cause paralysis of the larynx.

Influenza bacilli may be found alone, but they are usually mixed with cocci in the contents of the larynx as well as in the mucous membrane. Staphylococci especially, but also pneumococci, are found in pseudomembranous inflammations; mixed infections occur in ulcerous forms of inflammation (pneumococci, staphylococci, streptococci and influenza bacilli). Influenza bacilli alone, diphtheria bacilli alone, or both may be found in the croupous changes.

The reports on influenza of former years do not contain such detailed descriptions of laryngeal changes, as were given in the last epidemic; there are no descriptions of the croupous and ulcerous changes in the reports from the year 1890. These changes probably did not occur then.

Trachea and Bronchi.—The changes described in the larynx were manifold, and this is true of those in the trachea and bronchi. Those of the trachea and the large bronchi can be dealt with at the same time. They are best divided according to Askanazy. He describes the first change as the simple reddening and swelling of the mucous membranes.

He said the second change is catarrh; in this stage, the changes mentioned are combined with the appearance of mucous masses, which contain few leukocytes. It is interesting that in the wall of the respiratory passages, the infiltration consists mainly of lymphocytes and plasma cells with an occasional admixture of eosinophils. This lymphocytic infiltration may be so pronounced that the accumulations of round cells resemble lymph nodes. The superficial epithelium usually appears desquamated in the sections. As the third type, Askanazy designates those changes in which squamous epithelium appears on the surface of the mucous membrane. These parts, after removal of the mucus, appear as if they were "covered with a thin milk layer or a fine porcelaine base." Histologically, small islands, as well as greater stretches of stratified squamous epithelium, may be demonstrated. This change constitutes a true metaplasia. The fourth type of change is the necrotizing (pseudomembranous). It does not occur as a continuous membrane, but in the form of islands which make the mucous membrane appear granular. It is difficult to remove these membranes. These forms may occur, as mentioned, together with similar changes in the larynx or as their continuation. The necrosis may reach into the submucosa. Compared with true diphtheria, the amount of fibrin is small.

In all these conditions the mucous glands of the trachea and large bronchi also show catarrhal lesions (Scheimann), which may progress to a complete atrophy of the glands. Phlegmons may occur around the glands.

There are interesting changes in the lymph nodes of the trachea and large bronchi. They show, first, a swelling and redness, also hemorrhages. These changes may be found comparatively early in the disease, and may extend to the axillary and cervical lymph nodes. It has been said that these changes "frequently constitute the only form of the disease" (Schmieden). At any rate, it would be advisable to look for such changes when the relation to influenza is doubtful (intestinal form, nervous form or encephalitis). Histologically, edema, widening of the sinus and desquamation of its endothelium, sometimes hemorrhages, are found.

The bacteriologic examination may reveal only influenza bacilli in the trachea and large bronchi, especially in early stages of the disease; if the disease lasts longer, other types of bacteria are also found as a rule. Numerous streptococci are prominent when pseudomembranous changes occur. The lymph nodes frequently contain only influenza bacilli, but other bacteria may also be present.

Involvement of the parts of the respiratory system considered was known in former years, especially the occurrence of catarrh. Histologic investigations of these parts had also been made. For instance, Leichtenstern points out that the lymphocytic infiltration of the wall of the tra-

chea has been designated by Kuskow as "small lymphomas." Ribbert reports changes in the mucous glands. Apparently, however, not all the forms of inflammation mentioned have appeared in every epidemic; for instance, it seems that the pseudomembranous form did not occur in the epidemic of the nineties and in the epidemics of the following years.² In former epidemics, however, croupous changes are said to have been observed; Askanazy points out that Nonat demonstrated them in the epidemic of 1837.

The lesions of the smallest bronchi appear first in most cases of influenza. The bronchi are dilated and may be seen on the cut surfaces as small yellow spots or cavities. The contents consist in most cases of thin pus which flows without application of pressure. Sometimes, however, especially in the beginning of the infection, glasslike plugs or a viscid substance resembling fibrin may be found in the bronchioli. The dilatation of the smallest bronchi, attributed to a neuromuscular lesion, is called acute cylindric bronchiectasia and regarded as the effect of atony of the bronchi. Clinically, it may lead to the same phenomena as stenosis of the larynx, because expiration becomes impossible. It causes an acute, sometimes interstitial, emphysema and ultimately death by suffocation (Lubarsch). This purulent bronchitis and bronchiolitis is the gravest change caused by the virus influenza. The inflammation progresses from the affected bronchioli to the adjacent pulmonary tissue, and the so-called acinous bronchopneumonia arises. The suppuration, however, may progress from the bronchus, with resulting suppuration of the lung, or the originally catarrhal pneumonia may change into a purulent form. In both cases, smaller or larger abscesses may occur, either directly or during the intermediary stage of pneumonia. Histologic examination of the bronchiolus with such changes shows the following, according to Hübschmann: In the interior there is first a large mass of leukocytes, and between them or contained in them are masses of influenza bacilli. The largest part of the surface epithelium is desquamated; the epithelium which still adheres is also infiltrated with leukocytes. The influenza bacilli penetrate from the desquamated parts below the remnants of the epithelium, between the epithelium and the rest of the wall (Pfeiffer). Besides these changes, round cell infiltration is found in all the layers of the bronchial wall. In advanced cases, the infiltration consists of plasma cells. These infiltrations extend into the peribronchial tissue and reach the vessels there, which they cover in the form of mantles. They constitute an especially characteristic sign of influenzal bronchitis and bronchiolitis. The smaller the bronchus, the more massive are the round cell infiltrations. They divide the muscula-

2. Kaufmann is the only one who mentions in his textbook (1904) that diphtheric inflammations of the trachea and bronchi rarely occur in influenza.

ture of the bronchus so that there can be no possibility for any muscular activity. Together with the neurogenic paralysis of the bronchial wall due to the poisons of the agent of the influenza, these infiltrates are the main cause of the atony of the bronchi and of the subsequent acute cylindric bronchiectasia.

This bronchitis may result in pneumonia and chronic bronchiectasia. The obliterating bronchiolitis is an especially interesting end-result and, according to Hübschmann, may start comparatively early in influenza and originate from the alveolar exudate. Finally, induration due to collapse may also develop near the occluded bronchi. Proliferation of bronchial epithelium is a most peculiar feature; the cells grow especially into the alveoli and may assume the aspect of adenomas, even of carcinomas.

The contents of the small bronchi furnish the material of choice for the bacteriologic examination by the pathologist. The influenza bacilli may more easily and more probably be found in pure culture here than anywhere else; therefore, bacteriologic examination for influenza at necropsy should start here. It is self-evident that in advanced cases mixed infections will be found also.

Bronchiolitis was observed in former epidemics. Leichtenstern says that viscid, whitish yellow plugs appear on the cut surface of the lung on slight pressure, and he quotes Kundrat who reported that the patients were suffocated by these plugs. He refers further to Pfeiffer's sentence in his classic work on the etiology of influenza: "In the fine bronchi and in the pulmonary tissue, the influenza bacillus reigns alone." The description of the histologic changes in the lumen and epithelium of bronchioli just given was first published by Pfeiffer. These phenomena, which are regarded as characteristic of influenza, have been well known to former observers—at least, to those of the nineties.

Lungs.—Of the changes that occur in the parenchyma of the lungs in influenza, pneumonia is the most important. According to Kuczynski and Wolff, who based their opinion on the investigation of Dietrich, a primary influenzal pneumonia may be assumed. Besides the miliary bronchopneumonia, the lobular cellular inflammatory infiltrations as well as the edematous, hemorrhagic exudations must also be considered among the changes. These changes can be caused by the influenza agent alone. All other forms are regarded as complications, or products of mixed or secondary infections.

Marchand distinguishes the following anatomic forms:

1. "Minute acinous foci" is the designation given by Hübschmann to miliary bronchopneumonic foci originating in the bronchi. These foci are grayish red or yellowish, except in the center, which is yellow. The yellow spot corresponds to a suppurating bronchus. The yellowish hue

of the focus is due to fatty degeneration of the exudate. The alveoli are charged with leukocytes, proceeding from exudate in the bronchioles. The alveoli contain only a small amount of fibrin. Hübschmann thinks these foci are characteristic of influenza.

2. In multiple confluent lobular pneumonia, the foci are confluent and larger and are brownish, with a tendency to bleed. This form is the most frequent in influenza.

3. Suppurative bronchopneumonia is characterized by multiple necrotic and suppurative foci, varying from the size of a hemp seed to that of a pea, and formed of purulent bronchioles.

4. Large suppurative foci are sometimes wedge-shaped, sometimes jagged. They may be numerous and are seen on the surface of the lung. Absence of vascular thrombi in the vicinity indicates that the foci are not hematogenous.

5. In suppurative pneumonia, yellow stripes are found in the lungs at necropsy. They are caused by suppuration of the lymphatic ducts and surrounding tissues. This form is often secondary to empyema. The process may involve the pulmonary tissue. It shows a similarity to pleuropneumonia in cattle.

6. Hemorrhagic edematous infiltration is characterized by the presence of a bloody effusion in the pulmonary parenchyma. The fluid may be found also in the respiratory tubes and pleural cavities. The brown color of the effusion is the result of hemolysis. This form is most frequently observed in influenza occurring during pregnancy or the puerperium.

7. In lobar pneumonia there is a special tendency to suppuration. Oberndorfer, Glaus, Fritsche, Strassmann and Koopmann think that the first stage of influenzal pneumonia is characterized by a hemorrhagic lobular form.

Besides these forms, there is also the indurative desquamative pneumonia or carnifying inflammation of the lung. This may be primary, it may occur in the early stage of the disease or later, developing secondary to a catarrhal form. Weichselbaum first, and Ghon later considered desquamative pneumonia as typical for influenza. Pulmonary lesions may be present in various forms in the same patient. Association of these lesions with those in other parts of the respiratory system results in a variegated picture, characteristic of influenza.

The changes that have been described were not found with the same frequency by all investigators. The lungs, however, appear always to have been involved bilaterally. Summing up, it must be admitted that a form of pulmonary inflammation specific for influenza does not exist, for all the forms described may appear in other conditions as well.

Lobular pneumonia with a tendency to suppuration and hemorrhagic edematous and indurating inflammations must be regarded as characteristic of influenza.

Of the pulmonary changes of noninflammatory nature that may be encountered in influenza, emphysema must be cited. It has been mentioned that in capillary suppurative bronchitis, the alveoli became distended because of the impossibility of respiration, owing to bronchial atony. This results in acute substantial emphysema. If the pressure is further increased, the air leaves the alveoli and enters the interstitial tissue. This form of interstitial emphysema may also be encountered in influenza. Interstitial emphysema may extend from the lung to the surrounding structures; it is not unusual to see the mediastinum permeated with air bubbles.

Just as the paratracheal and tracheobronchial lymph nodes exhibit changes in tracheal and bronchial involvement, so the intrapulmonary lymph nodes are involved in changes of the parenchyma of the lung. In catarrhal pneumonia they present a simple lymphadenitis, but in suppurative or hemorrhagic pneumonia they may be the seat of suppurative or hemorrhagic inflammation.

It would now appear natural to try to bring the results of bacteriologic examinations of the pulmonary lesions into harmony with certain anatomic changes. The action of the influenza virus alone can be held responsible for the acinous and hemorrhagic edematous forms as I have mentioned. What is the situation in regard to the other lesions? Most of them are the result of mixed infections, that is, infections with pneumococci, *Micrococcus catarrhalis*, the various forms of streptococci, or staphylococci, with or without the influenza bacillus. In what manner are the various micro-organisms distributed in the different lesions? Ghon says:

In the pneumonias, the infection was practically always mixed or secondary. The suppurative interstitial pneumonias were always caused by *Streptococcus pyogenes*, the cases with suppurative peribronchitis or suppurative bronchopneumonia by *Staphylococcus pyogenes-aureus*. In 13 per cent of the cases of confluent pneumonias *Streptococcus mucosus* was found, in most of the rest *Streptococcus lanceolatus* (Pneumococcus). In necrotizing bronchitis *Staphylococcus aureus* was present.

Observations that agree with these statements have been made in respect to interstitial pneumonia, which is said to be caused by streptococci. Hübschmann agrees with Ghon as to the staphylococcic origin of the suppurative form of lobular pneumonia. Kuczynski and Wolff found staphylococci and streptococci in these foci. Marchand and Herzog found only streptococci. In the parts of the pulmonary parenchyma that had undergone hemorrhagic edematous changes, Marchand and Herzog and also Hübschmann found only streptococci in the tracheal and

pleural contents under these conditions. The pneumococcus was almost always discovered alone in the foci of lobar pneumonia.

Although agreement is not general it does obtain in regard to certain points. The influenza bacillus is found in the lung tissue, for instance, only in entirely early cases. It is most likely to be discovered in or close to the bronchus located in the center of the pneumonic focus. In the foci of lobular pneumonia the pneumococcus was present in pure culture in most cases. The suppurative foci of lobular pneumonia usually contained the staphylococcus, less often both staphylococci and streptococci, or the latter alone. In the interstitial suppurative foci and in the hemorrhagic edematous infiltrates only streptococci are discoverable. To the presence of the latter or to their hemolytic properties the brown color of the exudates may be ascribed. Descriptions of pneumonic changes have always occupied the largest amount of space in treatises on influenza. They are described by pathologic anatomists, such as Kundrat, Marchand, Ribbert, Schmorl and Weichselbaum in the nineties, as well as by the clinicians. Ribbert found lobular as well as lobar pneumonia, but he states that the former differed from the usual type by the fact that the cut surfaces were smooth and only rarely granular; they also appeared always to be divided into lobules. In his opinion, although the pneumonia is not specific, it is nevertheless characteristic for influenza in the frequency of the interstitial process, in the richness in cells and poorness in fibrin, in the histologic picture and, macroscopically, in the tendency to the formation of abscesses, necrosis (gangrene) and induration. Finkler described as influenzal pneumonia pulmonary inflammations characterized by active small cell infiltration of the peribronchial and interalveolar connective tissue and endeavored to separate them from the usual forms. (Hübschmann's description under bronchiolitis). Marchand described lobular and interstitial pneumonia with formation of abscesses; the lobular form showed brownish red parts; the lobar was remarkably soft, with little fibrin (microscopic). Pfeiffer, in his first report, described the lobular form of pneumonia as characteristic of influenza. It was his opinion that lobar forms were caused by the confluence of small foci; their origin in the lobular forms could always be recognized by the yellow centers and the pus filling the central bronchi. The lower one descends in the air passages, he says the more often does one find the influenza bacillus in pure culture. In the final stage of these influenzal pneumonias, according to Pfeiffer, miliary suppuration, induration, gangrene and direct caseation (in combination with tuberculosis) occur. Wassermann agrees with him and says that influenzal pneumonia has nothing in common with genuine croupous pneumonia, but is an independent form. Leichtenstern believes that a primary influenzal pneumonia occurs. The anatomic form of this true influenzal pneumonia, he says, is, according to Pfeiffer, Beck and

Wassermann, an exclusively catarrhal lobular pneumonia. Traces of fibrin are found in it. But there are also fibrinous forms, Leichtenstern holds, which arise from mixed infection with the pneumococcus, and, finally, mixed forms of lobular catarrhal and lobular fibrinous pneumonia, which, according to Weichselbaum, can be caused only by the influenza bacillus. The researches of Hübschmann follow; he directed attention particularly to the acinous or miliary bronchopneumonic foci. It is evident that no important differences were observed in the pneumonic changes that occurred during the various epidemics. In the earlier epidemics, as well as in the more recent one, the lobular form of pneumonia, with its tendency to formation of abscesses, hemorrhages and induration, was considered characteristic of influenza, particularly when associated with suppurative capillary bronchitis. The last epidemic, however, differed from the earlier ones in the severity of the pneumonic changes. The differences, especially in comparison with the epidemic of the nineties, were differences only in degree, not in kind.

The bacteriologic studies that followed Pfeiffer's discovery alternately confirmed or failed to confirm his observation in respect to the pneumonic changes. In the course of my own investigations I was impressed by the presence of staphylococci in the pneumonic changes, an unusual observation, in which view Hübschmann concurred. The highly developed bacteriologic technic of the years just preceding the war had failed to yield any similar observations. It cannot be decided with certainty whether or not the discovery of staphylococci reported by a few investigators during the nineties rests on technical errors, but in view of the technic of that time, a certain skepticism does not seem misplaced. Therefore, I should be inclined to view the appearance of staphylococci in the suppurative foci of lobular pneumonia as unusual and peculiar to the last epidemic.

Pleura.—Of the changes in the respiratory tract, only those of the pleura remain to be discussed. In the first place, there are extravasations of blood, which vary in size, but which often occur in the form of punctate ecchymoses. The true inflammatory changes are due to extension of pulmonary inflammation or, in the absence of that, to inflammation of the bronchi. The latter condition, in which the pulmonary parenchyma is not inflamed, is regarded as highly characteristic of influenza. The forms of pleuritis occurring in influenza are the fibrinous, suppurative, ichorous and hemorrhagic. Pure necrosis of the pleura may take place over the suppurative or necrotic portions of the lung tissue. Empyema develops as a sequela of suppurative inflammation. On a number of occasions attention has been called to the small amount of fibrin in the pleural exudate in influenza in comparison with the amount in similar conditions with a different etiology. In a few cases, pyopneumothorax also was found. The brief interval between the

onset of the disease and the development of pleuritis in some cases is remarkable. It seems that in the last epidemic the pleural changes were particularly frequent; Reiche, for instance, speaks of pleuritis as a complication "which stamps this epidemic."

The process may extend from the pleura to the cellular tissue of the mediastinum, to the pericardium and then to the peritoneum, and there it may give rise to similar changes.

The influenza bacillus rarely exists alone in pleuritis; in most cases the streptococcus was found, either associated with the influenza bacillus or, more often, alone. Next in frequency came the pneumococcus, alone or with the streptococcus. The staphylococci were the least frequent. Comparatively often the effusion was sterile.

Leichtenstern states that pleuritic involvement was a frequent complication of influenza in the nineties. Still earlier there was a so-called primary pleuritis, that is, one in which neither pneumonic changes nor abscesses could be demonstrated; Ribbert states that bronchitis was absent in these cases. The influenza bacillus was present in the exudates in pure culture, or there were mixed or secondary infections. Leichtenstern notes as a particular form, a "pleuritis grippalis," a hemorrhagic variety, the exudate of which was said to resemble "wine cream" or "clay water" and to contain the streptococcus in pure culture. This is the same change, it appears, that was described by Marchand and Herzog.

Thyroid.—The changes in the thyroid are scarcely mentioned in modern literature, and Leichtenstern says merely that strumitis has been observed a number of times following influenza, as after other acute infectious diseases.

The question now arises whether there are any changes that are specific for influenza. The answer is, no. From the anatomic changes of suppurative bronchiolitis, suppurative bronchopneumonia and induration pneumonia, even with the help of the anamnesis, the most one can do is to make a probable diagnosis of influenza. Certainty comes only with the demonstration of the exciting cause, in the form either of the influenza bacillus or of the filtrable virus.

GENERAL EFFECT OF RESPIRATORY INFLUENZA

When the respiratory apparatus is attacked by influenza, the entire body can, of course, become secondarily involved. This may be due to the spread of the micro-organism itself or to the inundation of the body by the toxins produced by the virus or its concomitants. Kuczynski and Wolff sum up the experiences of the last epidemic as regards the spread of the micro-organism by the blood stream: "Influenza bacilli are seldom demonstrable in the blood. Of other bacteria, the various cocci enter the blood in varying numbers in the different groups of diseases." But these

"septic" forms of influenza seem to occur rarely in relation to the number of necropsies. Spread of the exciting organism by continuity is of course also possible, for instance, from the pleura to the pericardium or from the nose, by way of the accessory sinuses or otherwise, to the meninges. In contrast to these rare occurrences, the changes attributable to the toxins are rarely absent. It is not easy to decide whether the individual changes are caused by the influenza bacillus or by associated micro-organisms or their toxins. Bacteriologic examination of the lungs, the blood or the organs in question is of course essential to the determination of this point. The effects of the toxins in influenza are seen chiefly in the circulatory system, the large parenchymatous organs and the central nervous system, while, as in other infectious diseases, the changes in the spleen are due to the presence of the virus itself.

Spleen.—Of the changes produced in the individual organs by influenza of the respiratory apparatus, most interest attaches to those in the spleen. In my own cases, which were cases of pure influenza, and which were nearly all rapidly fatal, I found the spleen scarcely changed. For the most part, it was not enlarged and contained a medium amount of blood; the earliest change was a slight softening of the parenchyma. In some cases, particularly in those of longer duration, the spleen was enlarged, but never greatly so. The reports of Borst, Miloslavich, Busse and Hübschmann agree with mine. Others, however, have commented on the frequency of splenic swelling. I would not insist on attributing the divergence in these reports to the difference in the extent to which other pathogenic organisms participated in the infection. The absence of swelling of the spleen in uncomplicated cases, however, seems highly important. It is known from pathologico-anatomic researches on the infectious diseases caused by filtrable viruses, that in the great majority of these infections the spleen is not swollen, and that the changes in that organ are insignificant. The circumstance that in pure influenza splenic swelling is usually absent, may be viewed as indicating that here also a filtrable virus is active.

Follicular swelling, hemorrhages, follicular necroses and hemosiderosis have also been demonstrated in the spleen in influenza. Bacteriologic examination of the spleen in influenza usually yields bacteria, but during the last epidemic, the influenza bacillus was seldom reported. On the other hand, it appears that the spleen may be sterile in spite of bacteria circulating in the blood. The bacteriologic examination of this organ seems to require further attention.

In the earlier literature there is the same lack of agreement regarding the behavior of the spleen that appears in reports of the last epidemic. Leichtenstern says that some investigators did not find the spleen changed, but that others frequently did. Kuskow found it

diminished in size, and considers this a characteristic of influenza. Leichtenstern attributes the occasionally swelling of the organ to infection by cocci. In his first report, Pfeiffer states that he demonstrated the influenza bacillus in the spleen in a few cases.

Circulatory System.—The circulatory apparatus is always involved in influenza. The changes found here are, in the vast majority of cases, the work of toxic products, and only rarely the expression of an actual infectious process. Studies during the last epidemic showed that it is the small vessels, rather than the heart, that suffer the greatest injury.

The most frequent lesion of the pericardium is hemorrhage, particularly in the form of ecchymoses. It is due to the action of toxic substances. Inflammation of the pericardium results directly from the action of the influenza organism, it is seldom primary; it is usually a sequela of pleuritis. It may be fibrinous, fibrinopurulent or purely purulent. Hemorrhagic inflammations also occur. In the exudates, cocci of various sorts are usually present (as found in bacteriologic examination in pleuritis); the influenza bacillus is also found at times.

The muscle of the heart may present a variety of changes, but they are seldom important or particularly characteristic. Degeneration of the myocardium has been described in influenza; it may be parenchymatous or, more rarely, fatty. It may be circumscribed, appearing under the form of Zencker's degeneration (necrosis). Hemorrhages may be found in the myocardium. In consequence of the degeneration of the muscle, dilatation of individual segments of the heart may take place; one-half only may be dilated. Cocci have frequently been found in the necrotic foci. Interstitial myocarditis has been observed in isolated cases.

The most frequent change in the parietal endocardium consists in small extravasations of blood. Primary inflammatory lesions of the valves occur, but recurrences of earlier valvular diseases are frequently observed. Anatomically, the valvular inflammation is of the verrucous variety. In the recurrent forms it was not unusual for bacteriologic examination to yield the influenza bacillus; the rarer primary endocarditis during influenza is ascribed to the streptococcus.

The vascular changes are particularly important in the anatomic picture of influenza. They have been studied with special attention by Stoerk and Epstein. In the medium-sized arteries, in particular, they found marked changes in the elastica interna and muscularis, appearing in the latter as necrosis. The coronary vessels appeared to be particularly affected. The anatomic changes in the smallest arteries are not so evident as in the medium-sized ones; they are recognized by their consequences rather than directly. These consequences consist in numerous hemorrhages demonstrable in persons who have died of influenza and in the hemorrhagic inflammation in this disease.

Thrombi are found in various parts of the vascular system. These, however, may be regarded, not as primary, but as the consequence of the mixed infections so frequent in this disease. Research at the time of the last epidemic failed to bring an understanding of the details of the vascular changes which, even during life, are so clearly shown in circulatory disturbances leading to cyanosis, lowered blood pressure and other symptoms, and which by numerous hemorrhages may give the anatomic picture its character.

In the earlier literature, particular importance was given to lesions of the organs of circulation (Leichtenstern). Then, as now, they were chiefly ascribed to the toxic products of the influenza bacillus, and the pronounced hemorrhagic tendency of influenza was commented on.

The changes in the individual parts are described in the older reports almost exactly as I have given them. The forms of pericarditis, the areas of degeneration in the muscle of the heart and the consequent dilations of the ventricles were likewise described. Metastatic abscesses in the myocardium were mentioned. It was said that endocarditis was seldom primary, but frequently secondary to changes in the respiratory tract caused by mixed infections. The influenza bacillus was not found in the endocarditic deposits at that time. Finally, thromboses were noted in the arteries, veins and the sinus of the dura mater, as were also phlebotic changes. Venous thrombosis is described as frequent; arterial thrombosis as comparatively frequent. Leichtenstern is of the opinion that a certain percentage of these thrombotic vascular changes must be looked on as primary.

Liver.—Among the other organs of the body that may be sympathetically involved in the disease of the respiratory system is the liver. As in most infectious diseases, the hepatic changes in influenza are not characteristic. For the most part they are not pronounced and consist chiefly of parenchymatous degeneration. Fatty degeneration was found more rarely; it generally appeared in the center of the lobule and was often circumscribed. Icterus was often described in the liver as well as in the entire body. Central necroses are designated as rare. Septic cholemia ending fatally was described by Flüßer.

In the earlier epidemics, according to Kuskow, changes occurred in the liver, such as hyperemic conditions, degeneration, infiltration of small cells, necrosis, abscesses and thrombosis.

Kidneys.—The disease may involve the kidneys, either in the form of parenchymatous degeneration of varying intensity, or, more rarely, as fatty degeneration of the tubuli contorti. Inflammatory changes are also described, such as suppurative exudative nephritis, apparently in expression of the septic course of the disease. The occurrence of glomerulonephritis was noted in the last epidemic. Kuczynski describes the initial stages of this process, and characterizes them as "toxic swollen

kidney." He ascribes this lesion not to the influenza infection as such, but to a mixed infection with cocci. Fahr designates this change as exudative glomerulonephritis; he points out that these inflammatory changes of the kidney were to be seen in influenza in the soldiers in action, while in patients at home they were absent. They may be compared to war nephritis. Fahr also describes cases of circumscribed interstitial nephritis. It was pointed out by Dietrich that the influenza process apparently creates a certain predisposition to the later development of renal disease. Extravasations of blood are frequently found in the renal pelvis and in the bladder in influenza.

Degeneration of the kidney was noticed in the early literature, but appears to have been rare. Leichtenstern says: "The bacteria and toxins of influenza are not nearly so dangerous to the kidneys, as, for example, the toxins of scarlet fever, diphtheria, etc. The rarity of acute nephritis appears in the older statistics. . . ." On the other hand, late nephritis was not an unusual observation at that time (Dietrich). Hemorrhages of the kidneys and bladder occurred, just as in the last epidemic. The abscesses occasionally found in the kidneys could be referred to mixed infections. In a few cases, Pfeiffer found the influenza bacillus in the kidneys as well as in the spleen. Finally, inflammation of the bladder was mentioned in the older reports.

The last epidemic, therefore, is distinguished from the earlier ones by more extensive involvement of the kidneys. This difference, however, cannot be ascribed to the influenza itself, but to the particular circumstances of the epidemic, namely, to the exposures and injuries of active warfare.

Disappearance of cortical lipoids and extravasation of blood have been demonstrated in the suprarenal capsules.

Generative Organs.—Inflammatory phenomena were noted in a few cases in the prostate, seminal vesicles and epididymis. In cases of chronic prostatitis, the influenza bacillus, together with other bacteria, was found in the prostatic secretion.

There is frequent mention of hemorrhagic endometritis in the female genitalia; ovarian hemorrhages also occurred. A suppurative endometritis was a rare observation. In the earlier literature nothing is said about the suprarenal capsules. Leichtenstern mentions simple "orchitis grippalis," periorchitis and gangrene of the testis and penis as occurring in influenza. Special prominence is given to the lesions of the female genitals. Occurrence of the menses before their time, menorrhagia, clinical manifestations of the hemorrhagic endometritis described in the last epidemic, and the frequency of abortion are noted.

Muscles.—In the last epidemic, changes in the skeletal muscles were observed with relative frequency. Tears, hemorrhages and, especially,

Zencker's degeneration with or without hemorrhages are described. The last change involved the muscoli recti abdominis particularly; also the thoracic muscles and the diaphragm. The lesion was analogous to that seen in typhoid. Continuing the analogy with the changes in typhoid, I am inclined to attribute these changes in the muscles to the action of toxic substances. Anatomic observations are lacking for the myalgias so frequently seen by the clinicians and for myositis.

In the literature of earlier years one finds clinical descriptions of myalgia; chronic fibrous myositis is mentioned, as are hemorrhages in the musculature. Under the microscope, Kuskow found finely granular turbidity and loss of transverse striation.

It appears that Zencker's degeneration, particularly of the abdominal muscles, was a peculiarity of the last epidemic, and it was observed with comparative frequency.

Joints.—Metastatic suppurative diseases of the joints are mentioned in the recent literature. Leichtenstern refers to the frequency of polyarthritis as an accompanying phenomenon of influenza in the nineties.

Bones.—Suppurative processes in the bones were also observed in the last epidemic, and they are mentioned in the reports of earlier years. Raspberry colored marrow was frequently met with in the femurs of persons who died of influenza; the greater part of the marrow had usually undergone this change. Bacteriologic examination of the bone marrow (Müller) yielded the influenza bacillus in addition to cocci in a few cases, but usually there was only a mixture of cocci.

Blood.—In the blood picture of influenza, leukopenia is the first apparent change. During the first two days there is also lymphopenia, which changes to lymphocytosis. The leukopenia is most marked during defervescence, after which there is leukocytosis. The eosinophils disappear on the second day of illness and do not return until after defervescence. The behavior of the monocytes is the same as that of the neutrophils. At the time of defervescence plasma cells also appear in the blood.

Nothing is said of the bone marrow in the reports of earlier years. As to the blood picture, Leichtenstern states that some investigators reported leukocytosis, while others denied its occurrence. The disagreement on this point in the earlier reports and not entirely absent in those of recent years seems to be best explained by the circumstance that, apparently, the examinations were made at different periods of the disease. The earlier investigators also pointed out the peculiar yellow color of blood obtained by venesection, a phenomenon which might be explained by the hemolytic action of streptococci associated in the infection.

Skin.—The skin is not exempt from changes in influenza. General icterus has not infrequently been described; this may be regarded as

septic, since it is found particularly often with septic pneumonia. Hemorrhages occur in the skin, but they are much rarer than in the serous or mucous membranes. Rashes are often found, in mild as well as in severe cases. They may present the character of erythema, measles or urticaria; scarlatiniform rashes have also been described. On microscopic examination, perivascular infiltration of lymphocytes was found in the petechiae. Coccic emboli have occasionally been demonstrated as the cause of rash, but this genesis is not to be assumed with certainty for all cases; many undoubtedly originate on an angioneurotic basis. Herpes has frequently been described in influenza; this appears to be of importance as possibly throwing light on the herpes-like encephalitic virus. In rare cases, Quincke's edema was seen. Emphysema of the subcutaneous tissue may be due to extension from the mediastinum.

In the older literature, particularly that of the nineties, eruptions in influenza are reported so frequently as to suggest dengue. They appeared at that time in the greatest variety of forms. In earlier epidemics, likewise, eruptions were frequent; as reported by Wittich in the year 1580 and by Biemer in 1743. Herpes is mentioned by Leichtenstern as frequent in influenza. He notes, furthermore, that the hair became gray and that vitiligo appeared. Icterus of individual regions was apparently fairly frequent in influenza in early epidemics. Albrecht and Ghon describe phlegmons containing the influenza bacillus.

II. THE GASTRO-INTESTINAL FORM OF INFLUENZA

Any discussion of the changes in the digestive tract in influenza must be prefaced by the admission that it is not certain that a primary or independent disease of the gastro-intestinal segment of this system is caused by the organism of influenza. The presence of the influenza bacillus in the stool, which has been demonstrated a few times, is not of course, proof of the existence of a gastro-intestinal form of the disease, for in the respiratory form these bacilli may reach the intestine through the swallowing of sputum. Rather it tends strongly to show that the gastro-intestinal symptoms, like those of the circulatory system, are produced in the course of the influenzal infection of the respiratory organs by the toxic products of the organism of influenza or of other associated bacteria. The inflammatory changes found occasionally in the intestine can easily be regarded as secondary to those in the respiratory system. It must also be remembered that in the intestine it is not always possible to rule out superinfection with dysentery. In any case, the influenza bacillus has not yet been found in the intestine in changes of that sort. Furthermore, anatomic descriptions of cases of influenza in which changes in the gastro-intestinal tract exist without concomitant changes in the respiratory organs will hardly be found. One must there-

fore regard gastro-intestinal influenza as chiefly a clinical conception, and understand by the term a form of the disease in which gastro-intestinal symptoms dominate the clinical picture. To the mind of the pathologic anatomist influenza will always appear in the sense of its usual form (originating in the respiratory system), and he will content himself with pointing out the more or less prominent participation of the gastro-intestinal tract in the process.

The influenzal lesions seen in the mouth, on the soft palate, on the tonsils and in the pharynx were included in the comment on the respiratory system, because it was assumed that influenza of this segment of the digestive tract originated in its other function, namely, the respiratory. All that is known of involvement of the next segment, the esophagus, is that in a few cases a pseudomembranous inflammation of the pharynx has extended into the esophagus.

Changes in the wall of the stomach are also rare in influenza. The most frequent are extravasations of blood in the mucous membrane. The term "hemorrhagic erosions" is applied to them, and they are found chiefly in the fundus. Acute gastritis, that is, redness and swelling of the mucous membrane, and localized necrotic (pseudomembranous) gastritis, which may descend from the esophagus, have also been described.

Only simple hyperemia or catarrhal inflammation is found in the intestinal canal in cases of influenza. Follicular swelling and dysenteric changes in the lower part of the small intestine have been observed. The contents of the large intestine occasionally have been designated as watery. Follicular necrosis has also been reported. Although in the last epidemic the intestinal complications of influenza were rare in adults, they were more frequently observed in children. Involvement of the appendix in influenza deserves special attention, because it played a certain rôle in the older literature. In the last epidemic the occurrence of epityphlitis (inflammation of the cecum), was reported, but appendicitis was not. A connection between these diseases and influenza could not be definitely established, however. It was also reported that in a few cases the clinical symptoms pointed to appendicitis, but that at necropsy the cause for these symptoms was discovered in a diaphragmatic pleuritis of the right side, in pneumonia of the right lower lobe or in a neuritis of the iliohypogastric nerve ("pseudo-appendicitis").

There are several ways in which the inflammatory changes seen in the peritoneum during influenza might arise. The most frequent mode of origin is probably extension of inflammation from the pleura or pericardium. A metastatic origin from pneumonia is also possible. Finally, peritonitis could have its source in the diseased intestine. An inflammation thus derived is almost always purulent, and as a rule the streptococcus is the only organism found.

The gastro-intestinal form of influenza, which was scarcely recognized as such in the last epidemic, played a more important rôle in reports from former years, at least in the reports of clinicians. Leichtenstern writes:

In most cases of influenza symptoms originating in the digestive apparatus are trivial and limited to loss of appetite while the fever lasts. There occur forms, however, in which the gastro-intestinal phenomena dominate the disease picture, respiratory symptoms are wholly absent and the nervous symptoms, such as headache, do not rise above the level of the usual "stomach headache."

As to the anatomic picture, Leichtenstern states that influenza may lead to acute hemorrhagic gastritis and enteritis. In accounts dating from this time the pathologic anatomists (Jürgens, Klebs and Lubarsch) describe severe ulcerous or hemorrhagic lesions of the gastric and intestinal mucosa, or ulcerations of Payer's patches with swelling of the mesenteric lymph nodes. Finally, Kuskow mentions "hyperemic" inflammations ending in necrosis of the mucous membrane. Weichselbaum reports a case of croupous enteritis, in which diplococci were found. It must be added, however, that Ribbert affirms that the reason that anatomic intestinal symptoms have infrequently been described is that usually they have not been looked for.

Leichtenstern classifies hemorrhage of the intestines with epistaxis and influenzal hemorrhages, of the pharynx, larynx and bronchi. Furthermore, he holds that the "typhlitis and perityphlitis following influenza," figuring repeatedly in reports from all countries, was not appendicitis, as usually assumed, but a true inflammation of the cecum. He says further: "The severe forms of influenzal enteritis may lead to peritonitis." He is not certain whether or not peritonitis may arise in any other way. Regarding the bacteriologic observations, he states: "Proof of the presence of the influenza bacillus in the intestine in hemorrhagic enteritis or in the peritoneum in inflammation of that structure is as yet entirely absent."

It appears, therefore, that in their views on the gastro-intestinal form of influenza, contemporary investigators have not departed so far from those of the older writers; rather, the early authors, particularly Leichtenstern, had a far-reaching understanding of the pathogenesis of influenza, limited, of course, by the bacteriologic knowledge of that time. Therefore the opinion that gastro-intestinal influenza represents chiefly a toxicosis from the poisonous products of the exciting organism of the disease, is still justified.

A word should be said concerning the parotid gland, which is included in the digestive system. Inflammations of this gland were reported in the descriptions of influenza epidemics of former centuries. Since, however, they were complicated by disease of the testes, Leichten-

stern thinks it possible that these cases may have presented a combination of influenza with mumps, to which view I am inclined to subscribe.

Changes in the pancreas have not been noted, either in the recent or in the older literature. Mittasch observed edema and in a few cases extravasations of blood in the pituitary body.

III. THE NERVOUS FORM OF INFLUENZA (INFLUENZA, NONA AND EPIDEMIC ENCEPHALITIS)

The changes of the nervous system in influenza must be considered in relation to the changes of the whole body. Are they subordinate to those of the respiratory system, or do they appear independently, which means primarily? Since, according to present views, the infection of influenza occurs through the respiratory tract, it is hardly possible for it not to affect these organs. One part of the respiratory passages at least must be penetrated by the germs before an infection of the nervous system can take place. Whether this necessarily entails disease of the respiratory passages, is as yet unknown. In some cases of nervous disease which occurred during influenza epidemics, pathologic changes of the respiratory passages were found, but apparently not in every case. And yet, participation of the respiratory system in the disease would be of great importance for the evaluation of relations of certain diseases to influenza. Naturally, in such cases the bacteriologic and serologic methods must be employed in addition to purely anatomic investigation. Serologic methods would reveal infection even if an anatomic lesion no longer existed. Therefore, these methods should be perfected.

It appears to be desirable to differentiate the nervous conditions that occur during or after influenza into those due to infection with the influenza agents themselves and those determined by the toxic products of the organisms or of the concomitant germs. It will be seen that it is not always possible to make a reliable differentiation, but it should at least be attempted.

In the following review the different parts of the nervous system will be considered from this point of view.

INFLUENZA IN PERIPHERAL NERVES

A question arises as to which form of influenza occurs in the peripheral nerves. Are there any processes which may be related to infection or to intoxication? It is not known definitely whether changes induced by the influenza agents themselves can occur in the peripheral nerves. For instance, one cannot exclude the possibility that, with acute inflammation of the lymph nodes of the hilum, from which influenza bacilli have been obtained, the causative agent may migrate directly to the vagus and produce neuritis. These conditions are not clear at present, since they have not been investigated. Therefore it is merely a

hypothesis that the changes in the peripheral nerves which cause the manifold clinical nervous symptoms are due to the action of a toxin. The results of neither recent nor earlier histologic examinations of the peripheral system in influenza are available.

MENINGITIS

The first changes in the central nervous system that I shall consider are lesions of the meninges.

Among the anatomic changes of the dura, especially regressive changes, necroses appear as sequelae of lesions in bone, for instance, in purulent otitis media. Among the disturbances of the circulation, hyperemia is seldom mentioned in the reports; hemorrhages of various extent are more frequent. There are transitions to hemorrhagic inflammations. On the other hand, cases of purulent pachymeningitis occur in influenza, probably always by continuity; it is likely that none of these lesions are hematogenous. The starting points for directly transmitted purulent pachymeningitis are inflammations of the accessory nasal cavities and of the middle ear, which are not rare in influenza.

The pia and arachnoid may be free from changes in some cases of influenza; in the great majority, however, these membranes are more or less red and moist. Hemorrhages varying in number and size occur. The principal pathologic conditions of these membranes are inflammatory. The anatomic picture is that of transition from an increased fluid content with a more or less pronounced turbidity to a purulent infiltration. Hemorrhagic forms of leptomeningitis apparently have not been described in the last epidemics. "Serous leptomeningitis" with various degrees of turbidity of the fluid between the soft membranes is not rare, and probably constitutes the anatomic substratum of the clinical conception of "meningism." Purulent meningitis is more rare. It may be transmitted by continuity from a similar condition of the dura and indirectly from the adjacent cavities (sphenoid bone, middle ear); or it may originate from the nose or pharynx by the way of the lymphatic vessels or by metastasis through the blood. Purulent leptomeningitis caused by direct progression will probably be most pronounced near the point of origin and spread gradually over the other areas of the cerebral surface, and thus point to the original focus. It is to be expected that the suppurations which originate in the nasopharyngeal space will establish themselves first at the base of the brain and the hematogenous processes at the convexity.

Study of the etiology of these meningeal processes in influenza shows that actions of toxic substances are apparently responsible for the hemorrhages, the hemorrhagic pachymeningitis, the redness and edema of the leptomeninges and for the serous leptomeningitis. On the other hand, the influenza bacillus will be found—sometimes in a pure

culture—in the pus of the meninges as the causative agent. It occurs more frequently associated with other germs, mostly cocci. Among the concomitant cocci are *Streptococcus pyogenes*, with its subspecies, *Streptococcus mucosus* and *Diplococcus lanceolatus*. Finally, cocci alone may be found in meningitis, usually a pure culture of streptococci.

Meningitis in influenza was well known in former years. Besides the forms just mentioned, Leichtenstern describes a hemorrhagic leptomeningitis. He draws attention to toxic inflammations, and believes that a primary meningitis occurs without changes in the respiratory system. He also mentions the convexity of the brain as the site of metastatic purulent leptomeningitis. In 1896, Ghon, who describes two cases of meningitis due to influenza bacilli, made a critical survey of the cases reported up to that time. Further papers and surveys on this problem have been contributed by Perez, Lorey and Martha Wollstein (influenza bacilli in the spinal fluid obtained by puncture).

While the changes of the meninges in influenza could be brought into relation to the causative agents of the disease, or to their poisons, the determination of a similar relation is not so simple in the condition of the central nervous system itself. An edema or hyperemia may be observed in the brain, but the brain may be without any changes. On the other hand, various investigators describe hemorrhages with varying frequency. The spinal cord only rarely shows changes similar to those in the brain.

HEMORRHAGIC ENCEPHALITIS

It will be best to recall the state of knowledge before the last great epidemic. The hemorrhagic form of encephalitis was considered characteristic of influenza. Leichtenstern was the first to call attention to the hemiplegias and monoplegias in influenza. They were caused by foci of an "acute hemorrhagic encephalitis." Although such hemorrhagic inflammations had been described before in other diseases, and consequently were not specific for influenza, later investigators, such as Virchow and Senator, Fürbringer and others confirmed them as a characteristic form, "encephalitis grippalis." These changes appear as distinct encephalitic foci which "consist of numerous thickly agglomerated minute hemorrhages resembling flea bites." They are situated mainly in the gray matter of the cortex and the central ganglions. Contrary to this, Leichtenstern claims that:

No unquestionable case has been reported in which acute encephalitis grippalis had caused an acute hemorrhagic superior or inferior polio-encephalitis by a localization in the floor of the third or fourth ventricle. All the reported cases of paralysis of the nuclei of the muscles of the eye developed after recovery from influenza, usually sometime later, without fever and without important cerebral symptoms, according to the type of degenerative neuritis and nucleoneuritis.

Wernicke described the clinical entity of hemorrhagic encephalitis (superior) as a syndrome in alcoholism. Following this, Strümpel regarded cerebral paralysis in children as due to an acute inflammation of the central convolutions, and later described another form with an atypical localization in the brain. M. B. Schmidt studied the so-called purpura of the brain. He introduced the term "ring hemorrhages."

An open capillary as axis or a capillary occluded by conglutinated erythrocytes, around it a necrotic hyaline zone, then a wreath of large epithelioid elements, proliferated cells of the glia and around it a hemorrhage forming a ring; this structure characterizes the purpuric spots in hemorrhagic encephalitis of the white matter.

He concludes:

Survey of all this material shows that the capillary hemorrhages developing under completely different conditions behave microscopically in a similar way, that in the three groups of diseases, namely, spontaneous purpura of the brain ("hemorrhagic encephalitis"), septicopyemic and traumatic hemorrhage, the ecchymoses of the white matter in the large majority of cases have the character of ring hemorrhages.

Schmidt regards these changes mainly as hemorrhages by diapedesis and attributes them to disturbances of the circulation in the afferent arteries. Cerebral purpura has recently been reinvestigated by Kirschbaum. He, too, found small cerebral hemorrhages in injuries and in toxic and in infectious processes. Yet he describes a cellular infiltration of the wall of the respective blood vessels or agglomerations of cells immediately around them. He observed the latter changes in traumatic-toxic hemorrhages (war gas poisoning) and in meningitis, abscesses and tumors of the brain. Dietrich assumes that general and local disturbances of circulation are the cause of the purpura that occurs in influenza. Borst does not regard the purpura of the brain as inflammation in the proper sense, and in the same way Spielmeier warns that purpura should not always be regarded as inflammation. Marchand and Herzog are opposed to the interpretation of such hemorrhages without other changes as signs of inflammation. Only Mittasch found cerebral hemorrhages with inflammatory changes in influenza, and he regards them as phenomena of a toxic inflammation.

From all the preceding facts it must be assumed that purpura of the brain in influenza is only in the rarest cases inflammatory. Therefore, it cannot be related to the causative agents of influenza, but must be regarded rather as an effect of the toxic substances that develop in this disease. What are the bacteriologic observations in these cases? Investigations during the last epidemic show that influenza bacilli could not be found microscopically (in smears or sections) nor by cultures from the brain. Mittasch reports that he cultivated influenza bacilli from

the brain. The brains in cases of influenza were as a rule sterile. Since the discovery of influenza bacilli, the literature reiterates chiefly the reports of two authors on the bacilli in the brain, namely, Pfuhl and Nauwerck, who are frequently quoted. If their papers are studied without prejudice, especially Pfuhl's, one must doubt the observations. For instance, when the authors say that pieces of tissue taken from the cadaver forty-eight hours after death were examined after another forty-eight hours, it appears improbable that influenza bacilli could still be found in them. In a similar way, when one reads that bacilli were found in the cytoplasm of ganglion cells or in the pancreas, or when it is reported that smears were made and bacilli found in a piece of spinal cord which had been kept for four months in Müller's fluid and which had become so soft that it was impossible to make sections, it is natural that doubt arises in regard to the reliability of the observations. Nauwerck's paper does not offer anatomic or bacteriologic proof of the existence of influenzal encephalitis with the presence of bacilli. One is strengthened in distrust of these reports by Ghon's paper in 1896, in which he criticizes in detail the observations on the central nervous system made up to that time. He finds that Pfuhl's and Nauwerck's reports cannot be considered proof of the existence of a special influenzal encephalitis with bacilli.

It appears from these considerations that purpura of the brain in influenza does not generally constitute an inflammatory change. On the contrary, it follows from the earlier and recent investigations that in most cases it is due to a disturbance of circulation. It also follows that definite and reliable evidence of the presence of the influenza bacilli in the brain in influenza has not been produced.

EPIDEMIC ENCEPHALITIS

If the condition in purpura of the brain in influenza is not perfectly clear, the relation between influenza and a disease which has recently been called epidemic encephalitis is still less so. At present two opposite opinions are held: one is that these phenomena are symptoms or sequelae of influenza; the other, that they constitute a specific infectious disease which should be differentiated from influenza. While the view that all the phenomena were caused by influenza prevailed in the beginning, it was abandoned almost universally after the reports on various organisms that were alleged to be the causative agents of epidemic encephalitis. More recently, the view that influenza and epidemic encephalitis are related has gained ground again. I shall therefore discuss the facts that tend to prove or disprove a relation between the two conditions.

History.—In the first place, the history of influenza must be studied, especially in regard to the question whether conditions resembling encephalitis occurred in former epidemics of influenza and whether epi-

demics of encephalitis alone occurred. As regards the clinical picture of epidemic encephalitis, an acute and a chronic stage must be distinguished in this syndrome. The acute stage is characterized by its polymorphism, the chronic by its uniformity. In spite of that, it is possible to describe certain types in the acute form. One type, which at first gave the disease the name "sleeping sickness," consists chiefly of a more or less prolonged sleep. It usually starts with or is accompanied by paralysis of the muscles of the eye. These paralyses may occur alone as the lightest manifestation of the disease. The second type of the acute form is characterized by a striking tendency to movement resulting in chorea or in a choreiform condition. The lightest expression of this form, observed especially in children and in adolescents, occurs as prolonged sleeplessness, which again is most frequent in children. Associated with those two main types, or forming transitions between them, are many nervous phenomena. The chronic form is characterized by rigidity of muscles, the so-called parkinsonism, salivation, hyperhidrosis and the "sebaceous face" (the face shining as if covered by fat because of increased secretion by the sebaceous glands).

The history of influenza shows that this disease has always been characterized by complication with stupor or sleepiness. From the oldest, hardly utilizable reports to the epidemic of the nineties, this symptom is always mentioned as a concomitant condition or sequel. For instance, Wittich and Sennert report that in the influenza epidemic of 1580, a sleeping sickness occurred in Saxony and Italy; Fechtius mentions "*Morbus epidemicus per totam fere Europam Schloffkrankheit dictus*," and Brunner, "*von dem unüberwindlichen Schloff und von den Schlucksen*" (sleep and hiccup). Willis (1658) mentions sleepiness as a symptom of influenza. Grimm (1667) talks about the sleepy fever of children, Sydenham (1675) of the "*febris comatosa*." Ozanam emphasizes it in the epidemic of the year 1691. Camerarius describes sleeping sickness in Tübingen in 1712. Ozanam, in Berlin, in 1718; Beccaria, in Bologna, in 1729. Ozanam further reports an epidemic of "*soporosité*" in 1745 in Germany, another in 1800 in Lyon and an identical one in 1802 in Milan. Lepecq de la Cloture reports that in 1768 he observed in a "*fièvre putride miliaire*," which followed an influenza, frequently "*des assoupissements léthargiques, du coma somnolentum*." Sleepiness was also frequent in the epidemic of 1830-1833. Graves reports that he saw in the influenza of 1843 signs of erethism and signs of depression; the latter were observed in comatose conditions. In Ziemssen's "*Handbuch*," published in 1874, it is noted that lethargy characterized most of the epidemics of grip.

The history of "*nona*" from the year 1890, however, seems most interesting. This name designates a disease which occurred at that time

in Italy, and which manifested itself by sleepiness. It is a remarkable fact that this Italian "nona" seems almost to disappear, if investigated closely, as Longuet remarked, but reports on the subject have been published in many countries, and have not attracted any attention. From the literature the following picture may be reconstructed:

In the year 1890, the newspapers brought many reports of a disease raging in Italy near the Austrian frontier, in which the patients died after a prolonged coma or sleepiness. An English physician, in Italy at the time, tried to get better information about the epidemic, and applied to the secretary of the interior in Rome. This office requested immediate reports. The result was that in the province of Mantua four communities reported one case each in which there had been symptoms of lethargy and delirium. Influenza had preceded in three of these cases; in one case typhoid was incriminated. All these patients are said to have recovered. An Italian investigating commission later declared that the whole disease was a "*febbre esantematica migliariforme contagiosa*." This expression partly refers to Lepecq de la Cloture's nomenclature and partly reminds one of Leichtenstern's report that striking rashes frequently occurred in the epidemic of the nineties.

Not much has been left of "nona"³ in Italy. In the meantime, however, reports on similar cases appeared in many countries, and the anatomic basis of this disease excited interest. Only the Viennese neurologist, Mauthner, took the Italian reports as an occasion to create a theory concerning sleep. With prophetic intuition, he localized the anatomic lesions in sleeping sickness in the gray matter of the third ventricle and of the aqueduct, where they were found thirty years later by von Economo in the disease called by him "*encephalitis lethargica*." The reports on similar cases originated in Bulgaria, Germany, Austria (Bohemia and Vienna), Switzerland, France, Denmark, England and America. The most important literature has been collected by Longuet.

Tranjen, in Sistow, Bulgaria, observed three cases (two of them in children) of comatose conditions; one of them is said to have occurred without a preceding influenza; in the second case, the lethargy accompanied influenza; in the third case, it was a sequel. All three patients died. Necropsy in one case revealed only a considerable hyperemia of the meninges; the brain was edematous, but without other changes. In Bolkenhain, Silesia, Brown observed a fatal case in a girl, aged 14, without preceding influenza. Müller (Pforzheim) reported a case in

3. The origin of the word "nona" has been discussed considerably. Apparently, the editor of the New York Herald, who translated it "going asleep" or "falling asleep," has given the best explanation of this expression. The word "nona" is said to occur in the dialect of Naples and signifies the sleepiness of a grandmother (*nonna*).

a man, aged 51, two months after influenza, with recovery. Hammer-schlag, in Kolin, Bohemia, saw two cases in patients, aged 14 and 15, after influenza, with recovery. Priester, of Vienna, saw a case in a man, aged 54, one month after influenza, with recovery. Kaumheimer, in America, had one case of long duration after influenza. Hallager, in Denmark, described a case after influenza in a girl, aged 16, with recovery. Barret, in England, had a case after influenza in a child, aged 1. Frome Young, in England, saw a case in an older woman after influenza. Sharp of New York saw a similar case. Whipham (England) had two cases after influenza. Henry (Switzerland) had one case. Finally Longuet reports a case in a young man in whom lethargy appeared four days after influenza and ended in recovery.

Thus the disease designated "nona," which is generally assumed to be limited to Italy, could scarcely be found in that country, but occurred almost everywhere that influenza appeared. In the epidemic of the nineties, as in the numerous former epidemics, cases of lethargy were observed.

It may be pointed out further that Leichtenstern reports such cases from his own observation in his monograph in 1896. The paralysis of the muscles of the eye after influenza mentioned by him should be especially emphasized.

Two more cases of lethargy after influenza were described by Bozzoli, one occurred in 1895 and one in 1900. Besides the German cases, Kayser-Petersen mentions another reported by Salomonsohn (1891) and one by Freyhan (1895). A report by Martha Ulrich in 1911 appears to be of special importance.

A woman, aged 30, and her children had suffered from influenza in the beginning of October. Besides other nervous symptoms of moderate degree, she showed a striking lethargy. The sleepiness, accompanied by a high fever, increased to a sopor, and the patient died.

Confluent bronchopneumonia of both lower lobes, with a beginning fibrinous pleurisy on the left side, and venous hyperemia of the abdominal organs were found after death. Macroscopically, the brain appeared entirely normal. The substance of the brain contained much blood; the cortex was comparatively dark, sharply differing from the white matter. Microscopically, the brain and also the pia contained numerous foci of blood pigment and red cells near the blood vessels. The nuclei of the glia surrounding them were numerous; the ganglion cells moderately changed. Besides these small disseminated foci, the stem of the brain contained—chiefly near the blood vessels—a number of larger foci . . . which consisted of erythrocytes, blood pigment, detritus of nuclei, and of leukocytes, lymphocytes and mast cells. Two such foci were situated in the right thalamus, one in the right peduncle a larger number in the tegmentum of the peduncles, and several foci in the pons.

Not only lethargy was described as occurring in former epidemics, but also the opposite condition. For instance, Willis reports sleeplessness

as a symptom of the grip in 1658; Cammerer says about the epidemic in Tübingen that it was "nunc agrypnia, nunc veterno molestior." Sleeplessness was frequent in the epidemic of 1830-1833. Graves mentions signs of erethism in the epidemic of 1843. Insomnia is reported by Ebstein, Hellpach and Leichtenstern; there is no epidemic in which lethargy has been reported without a simultaneous mention of the opposite condition. Choreic phenomena are further noted by Zuelzer, Eichhorst and Leichtenstern. Finally, it may be pointed out that in the last epidemic the same extraordinary variety of nervous symptoms, partly under the name of epidemic encephalitis, has been reported in influenza (Leichtenstern).

Thus it appears that at least the main symptoms which in recent times have been attributed to the acute form of epidemic encephalitis, had been observed in all epidemics of influenza, especially lethargy; but isolated paralysis of the muscles of the eye and, on the other hand, insomnia and choreic symptoms had also been observed. In former times, it was attempted to separate the nervous phenomena occurring in influenza epidemics from the disease influenza, and an expression resembling very much the present "encephalitis epidemic" had even been selected by Sauvages,⁴ namely, the "cephalitis epidemica."

While the clinical manifestations of the former epidemics of influenza conform in their main nervous symptoms with the syndromes which now are separated under the name of epidemic encephalitis, it is evident that the same applies to the anatomic changes. From earlier times only Tranjen's and Ulrich's cases are known. In Tranjen's case, in which the brain had been examined only macroscopically, no changes were apparent. In Ulrich's case, gross anatomic changes were also absent. Yet, in her case, microscopic examination revealed true hemorrhagic encephalitis. The signs of inflammation were limited to the gray matter of the cortex and basal ganglions as they are usually found in epidemic encephalitis. There is therefore conformity clinically as well as histologically in cases of lethargy in influenza in former times and cases of so-called lethargic encephalitis at present. It is of some importance to point out that such cases occurred at the time of the great epidemics (Tranjen's case in 1890) as well during the time that intervened between them (Ulrich's case in 1911).

There are reports from former years of occurrences that correspond to the symptoms characteristic of the chronic form of epidemic encephalitis. Rigidity of muscles and paralyzes are noted in the old reports. Leichtenstern reports from his own experience a case of shaking palsy of a single extremity, and deals with others which had been

4. Encephalitis lethargica had also been used before. Ebstein found it in Berndt's "Fieberlehre" published in 1830.

reported by other authors. Cases of "typical paralysis agitans" are mentioned as direct sequelae of influenza in the German collective report on the epidemic of the nineties and by Bossers at the same time from the hospital in Amsterdam. Further, Leichtenstern mentions universal hyperhidrosis among the vasomotor-trophic neuroses following influenza. A careful investigation of the literature would certainly reveal further similar reports.

Relation to Influenza.—None of the reports of former years indicate that epidemics of encephalitis have existed without a simultaneous epidemic of influenza. Sporadic cases of encephalitis occurred between the widespread epidemics of influenza, just as did sporadic cases of influenza (Ulrich's case).

Accordingly the situation may be summarized as follows: Even if one or the other of the epidemics of former centuries now regarded as influenza perhaps was not influenza, there is such overwhelming evidence from observations which seem to be scientifically acceptable as to warrant the conclusion that phenomena due to a pathologic condition of the central nervous system have at all times followed epidemics of influenza, and that these phenomena that were separated in the last epidemics as encephalitis were identical in the various epidemics. It is not permissible, therefore, from the standpoint of historical research, to separate the nervous diseases of the last epidemic from influenza and to construct from them a separate entity. With knowledge of the older literature, it seems peculiar that a special causative agent has been sought in the etiology of the nervous symptoms.

In this respect there is agreement with the opinions of Ebstein, Gottstein and Kayser-Petersen, whose reports have been considered. These authors conclude that the historical data do not warrant a separation of the syndromes which have been called encephalitis from influenza. They suggest the term "grippal encephalitis" for the central nervous manifestations in question.

What was the sequence and local character during the last epidemic of both influenza and epidemic encephalitis? Von Economo and his followers always claim that the increase in cases of epidemic encephalitis (at that time still called lethargic encephalitis) occurred before the first great wave of the last influenza epidemic had started (1916-1917). It must be said that in former times such cases occurred before the onset of an extensive outbreak of influenza. The best example is Martha Ulrich's well studied case (1911). Besides this, one must remember that sporadic cases of influenza occurred between extensive epidemics and that an infection naturally always can start from them. Furthermore, it may be pointed out that Hübschmann recognized cases of influenza in Germany in 1915 and that Paltauf in the winter of 1914-

1915 drew attention to the influenza infesting the camps of war prisoners in lower Austria. Therefore, organisms of influenza were apparently present in Austria in the year 1916, even though there was no epidemic at that time. Therefore, the appearance of cases of epidemic encephalitis before the epidemic of influenza proper does not seem to be a valid reason for separating that syndrome from influenza. Besides this, according to Lucet's report, an epidemic of influenza characterized by prominent nervous symptoms had been observed in France in the years 1914-1916. In the subsequent years, 1918, 1919 and 1920, the encephalitic manifestations followed the various epidemics of influenza. They were not observed in Germany until after the appearance of influenza. Therefore, the sequence of the conditions in the last epidemics does not furnish a reason for separating them.

The question arises whether epidemic encephalitis is contagious as such. In Germany, not one unquestionable case of contact infection in epidemic encephalitis has become known. Some such cases have been reported from England, but some of them can be traced just as readily to influenza. It is known that Schlesinger especially pleaded that there was some relation between the diseases, and one of his cases apparently speaks strongly in favor of it.

A young man with the livid form of influenzal pneumonia was placed in a hospital room that up to that time had not contained a patient with influenza. He died after twenty-four hours. Necropsy revealed typical influenza. One day after his admittance, the other four patients in the room had high fever and pulmonary symptoms. Three of them developed marked disturbances of the sensorium, and one who died with the symptoms of epidemic encephalitis was proved on necropsy to have had typical influenzal pneumonia; two others recovered gradually; the fourth patient complained about four weeks later of twitching in the shoulder and headaches, and presented the picture of choreiform encephalitis.

The acknowledged slight contagiousness of epidemic encephalitis suggests the explanation that the cerebral symptoms in influenza are due to poisoning with toxic products of the germs. It could be further assumed that at a stage in which the phenomena of encephalitis become manifest the agents are no longer present in the body, so that the disease cannot spread.

According to their interpretation of the epidemiologic facts, some investigators decide for, some against, any relation between the two conditions. Von Economo was the first to insist on the separation of encephalitis as a disease *sui generis*, and a number of authors have followed him, especially those who reported discoveries of a special agent of encephalitis. Numerous other clinicians declared their opinion

that there is a relation between the two conditions and representatives of other fields joined them on the basis of epidemiologic investigations (Gottstein and Kayser-Petersen).

There is a further similarity between the two conditions in the predilection of both influenza and encephalitis for certain age periods. Leichtenstern reports that influenza attacks especially the youthful and strong. The same observation was evidently made during the epidemics at the end of the World War. In these epidemics also, the greatest mortality from influenza occurred in persons between the ages of 17 and 35. Statistics of cases in the Czechoslovakian republic reveal the largest number of cases of epidemic encephalitis in the same age period (from 15 to 30).

Microscopic Changes.—The anatomic histologic changes of the central nervous system are cited as another reason for separating epidemic encephalitis from influenza. Von Economo separated the changes in epidemic encephalitis into the so-called parenchymatous non-purulent or lymphocytic encephalitis and the hemorrhagic and purulent forms. He regarded the perivascular lymphocytic and plasma cell infiltration, the focal proliferation of the glia and the neuronophagy as characteristic of the acute form of epidemic encephalitis (at that time still called lethargic encephalitis). He also occasionally found hemorrhages of the usual type, and he believed that the changes were limited to the gray matter of the brain. His followers generally confirmed these observations; only the neuronophagy was not always found and was not acknowledged as specific for epidemic encephalitis. Single authors reported also that the changes described are not strictly limited to the gray matter, but that they may be found also, although in a much smaller degree, in the white matter (region of central ganglions). Few describe the presence of leukocytes in the infiltrates. Lucksch and Spatz pointed to the dispersion of the pigment from the ganglion cells in the region of the substantia nigra as a regular and therefore characteristic occurrence, even in cases of acute encephalitis.

The changes in the brain described in epidemic encephalitis may be found also in the spinal cord, usually only in the upper parts. They naturally resemble much the changes in acute anterior poliomyelitis, but differ from the changes in that condition partly because they are not so strictly limited to the anterior horns. Furthermore, if primary poliomyelitis spreads to the brain, the inflammatory changes in the spinal cord are naturally older (ganglion cells have disappeared in the anterior horns). The changes in poliomyelitis in the brain can always be recognized more or less distinctly as recent, and the presence of leukocytes, which are rare in encephalitis, may be of value for diagnosis.

Von Economo and his followers, in their attempt to separate epidemic encephalitis and influenza, emphasized especially the assumption that the

hemorrhagic form of encephalitis is characteristic of influenza. If it is borne in mind, as mentioned, that the changes in the brain in influenza as a rule are only the expression of the toxic injury of blood vessels, and that they do not constitute a true inflammation, then the dogma that hemorrhagic inflammation characterizes influenza collapses. This means that before epidemic encephalitis was studied, inflammation was not recognized as characteristic of influenza, but only as a toxic disturbance of circulation, the cerebral purpura. Yet capillary hemorrhages are not so rarely found in epidemic encephalitis. On the other hand, the pictures of the changes in the brain in influenza described by Mittasch (also partly by Siegmund) present distinct transitions from the changes of a cerebral purpura to those of epidemic encephalitis but with respect to the inflammatory lesions (lymphocytic vascular infiltrates) and to the behavior of the glia and the ganglion cells. It has to be admitted that Mittasch and Siegmund always found leukocytes in the infiltrates in epidemic encephalitis. Mittasch concludes from his investigations that transitions from both forms of encephalitis occur, and that they should not be separated. It seems that one of the histologic changes especially indicates some relation between influenza and epidemic encephalitis which does not seem to have been pointed out before. It is the lymphocytic or plasma cell infiltration of the walls of bronchi and the same structures of the perivascular infiltration in the exanthems of the skin in influenza. These characteristic changes constitute a striking analogy to the perivascular infiltrates in the central nervous system in encephalitis. Both changes are reported in the same way by all investigators as characteristic, and are practically identical. Although it is not permissible from this fact alone to accept the identity of the conditions, yet it is evident that it can at least be accepted as a link in the chain of proof of their identity.

The manner in which the different changes in the brain develop in those two processes might perhaps be explained best as follows: One might assume that during an influenza epidemic proper, cases of cerebral purpura may occur, indicating that acutely fatal cases are caused by an especially virulent factor at the acme of the epidemic. The hemorrhages in the brain would be the effect of toxic products which are especially marked at this time, and as such would parallel the hemorrhages in the rest of the body in influenza. The longer the influenza epidemic lasts, the milder become the morbid phenomena. Fewer hemorrhages are found in the brain and elsewhere in the body, and besides the hemorrhages with leukocytic infiltration, lymphocytic infiltrates in the walls of the blood vessels appear. In the further course, the hemorrhages become rarer and the infiltrations more plentiful. As the time from the acme of the epidemic becomes still longer, forms of cerebral inflammation will be found that consist merely of infiltrates of lymphocytes,

which is assumed to be characteristic of epidemic encephalitis, in which the lymphocytes are replaced more and more by the plasma cells. It is easy to imagine that these last changes are induced by a weaker poison in smaller doses which acts more slowly in contrast to the severe and acute lesions caused at the height of the epidemic by the powerful action of toxic products, which manifest themselves in numerous hemorrhages, as seen in hemorrhagic influenzal encephalitis.

It is believed that this opinion is confirmed by the fact that cases in which symptoms of encephalitis occur are comparatively rare during the height of epidemic influenza, while they increase in frequency as the epidemic recedes from the acme. On the other hand, they also occur before the epidemics, that is, at a time of less marked aggressiveness on the part of the causative agent.

The fact that the hemorrhages in influenza affect the white matter, too, even more than the gray matter, may be explained without much difficulty by the difference in these parts of the substance of the brain.

Consequently, the changes in influenza and in the acute form of epidemic encephalitis are connected by transitional forms. In order to prove a relationship between influenza and encephalitis, it seems necessary to investigate the condition of the central nervous system in influenza more systematically in the future than has been customary so far. Cases without purpura and cases in which the macroscopic examination does not reveal any changes must be investigated with special care; cases toward the end of an epidemic will be of great importance in this respect.

When dealing with the anatomic changes, a few words may be said about changes in the brain in the so-called chronic forms of epidemic encephalitis and its sequelae. The syndrome of parkinsonism, hyperhidrosis, salivation and a sebaceous face is not yet completely understood as to its anatomic basis. The investigations of Tretiakoff, L'Hermitte and Cornil, Goldstein, Spatz, Jakob and Lucksch and Spatz have shown that the cause of parkinsonism is to be found in the destruction of the ganglion cells of the substantia nigra. The anatomic substratum of the other striking vegetative symptoms of the chronic form of encephalitis has not been investigated as yet. Anatomic studies of such conditions were not made in former epidemics of influenza. Only clinical data on them exist. The fact that these phenomena have been observed so frequently in the last epidemics of influenza is due, beyond doubt, to the general situation created by the war.

Bacteriologic Observations.—Finally, in settling the question whether epidemic encephalitis is a disease *sui generis*, investigations of the etiology of the condition should be of the greatest importance. Cocci were first incriminated as etiologic agents, especially von Wiesner's *Diplostreptococcus pleomorphus*, found also by others; then protozoa

were found by Hilgermann and his collaborators. The opinion that the organisms just mentioned are the cause of epidemic encephalitis, has not been accepted. Of greater importance seem to be the discoveries of filtrable viruses as described at first by Strauss and his co-workers, then by Levaditi, Doerr, Kling and their collaborators, by Koritschoner and Bastai. The viruses discovered by Levaditi and by Doerr were shown by Doerr to be identical with the virus of herpes. Since this discovery by Doerr, the discussion has limited itself mainly to the question whether the virus of herpes is at the same time the agent of epidemic encephalitis. It is not possible now to deal with all these investigations, among which those by Flexner and Amoss are especially important because of their negative results. It might be sufficient to point to the result of the experimental research in Doerr's and Stern's reports at the meeting of microbiologists in Frankfort. According to Stern, the research did not settle the problem of encephalitis. He declares that it is improbable that the virus of herpes is the causative agent of epidemic encephalitis. The observations of others who described various forms of the virus of herpes are due, according to Stern, to confusion with spontaneous encephalitis of rabbits. Koritschoner's virus was identified as one of rabies. The encephalitis produced by cocci was either a spontaneous encephalitis of rabbits or a nonspecific inflammation of the brain (Stern). Even Doerr declares at the end of his report that it is not certain whether the causative agent of epidemic encephalitis is the virus of herpes or some other virus resembling it.

The results of etiologic research on epidemic encephalitis at present, therefore, are not such that they necessarily demand a separation of encephalitis and influenza. On the other hand, it must be mentioned that influenza bacilli have been found in cases of encephalitis, for instance, by Levinthal in the spleen, by Olsen in the pharynx, by Reinhardt in the lungs, by Manteufel in the nose and the trachea and by Elkeles in the lower part of the respiratory tract, and that Bieling and Weichbrodt have found agglutinins for influenza bacilli in the serum of patients with encephalitis. Although the presence of influenza bacilli does not prove the etiology of the disease, nevertheless the presence of agglutinins would at least support the opinion that an influenza infection also occurs.

Thus the results of etiologic research do not show that the so-called epidemic encephalitis is not a manifestation of influenza. Whether in these forms of encephalitis the hypothetical invisible form of the influenza agent plays a direct rôle or whether the phenomena are due to the action of the toxic products of the influenza agent or of the germs associated with this agent, is another question. This question necessarily leads to another, which may be answered later as the research of filtrable agents progresses. This question is how filtrable forms of

growth of pathogenic agents are related to the true toxins. Is it perhaps possible to see in the dissociation of infectious germs that do not form toxins something similar to the formation of toxins or at least to the liberation of endotoxins? Could identical or similar effects be caused by both processes? Are there perhaps continuous transitions from protoplasmic fragments and endotoxins to true toxins? It is known that other opinions have been expressed about the poisons that cause encephalitis. It has been assumed that poisons are not necessarily furnished by the invading organisms themselves, but that they may originate in the body under their influence. Fuchs considered the liver as the place of origin of poisons. Kuczynski and Wolff discuss such a secondary origin of the poisons. In continuation of these assumptions, Silberstein's experiments produced in dogs with Eck fistula transmissible encephalitis by feeding them with proteins. Furthermore, Rivers and Tillet as well as Andrewes and Miller, induced a transmissible orchitis in rabbits by injecting sterile horse serum. This leads to Rössle's investigations on aseptic inflammation, but further discussion of these conditions is not warranted at present.

Conclusions.—All the conditions that bear on the question of the relation between influenza and encephalitis have been considered. Special importance has been placed on the historical presentation of the question, because, while it is possible to differ about statistics and epidemiologic data and even about bacteriologic and anatomic observations, subjectivity vanishes when confronted with clear historical reports.

The facts in the history of influenza force one to assume a chronologic connection between influenza and the syndrome which has been called encephalitis. Even the epidemiologic experiences of the last great epidemic of influenza do not contradict the assumption that the conditions belong together. A transition between the lesions appears histologically possible. The etiologic and experimental research on encephalitis has not revealed a separate causative agent. The most probable opinion attributed the syndrome called epidemic encephalitis to the action of poisons that appear in the body in influenza. It is still uncertain what these poisons are. Accordingly, the correct designation for the nervous conditions would be "influenza encephalitis," and the term "encephalopathia postgripposa" (Jaksch) could be recommended for the late forms or sequelae with parkinsonism, and similar symptoms.

Among other forms of inflammation that may be observed in the nervous system in influenza are sporadic cases of purulent encephalitis (there are no records of purulent changes in the spinal cord). These purulent inflammations of the brain may be regarded as extensions from similar processes nearby and cases have been reported that were due to embolism of cocci. Influenza bacilli have not been demonstrated in the purulent processes.

SUMMARY

In summary it may be said that the anatomic changes in the last epidemic of influenza differ from those in former epidemics mainly in their seriousness, that is, quantitatively. In this respect, I may point to the changes of the respiratory tract and its appendages (pleura) and to the grave changes in the nervous system, the toxic injuries that manifested themselves, especially in the vascular system. The pathologic-anatomic changes during the last epidemic differed, however, from those in the former epidemics, not only quantitatively, but also qualitatively. Of the changes that are qualitatively different, may be mentioned the pseudomembranous inflammations of the respiratory passages and the metaplasia of their epithelium. The latter changes especially had not been recorded before. Regarding the bacteriologic observations, cautious mention is made of the participation of staphylococci in purulent processes of the lungs as something different from what occurred in former years. Anatomic changes of the digestive system were found still less frequently than before, if possible. A further peculiarity of the last epidemic seems to be Zencker's degeneration which was frequently observed in the rectus muscles. The most striking phenomenon of the last epidemic—besides the great mortality—is the frequent and grave participation of the central nervous system in the disease. Among these nervous changes, the chronic or so-called residual phenomena apparently have no predecessors of equal significance and frequency in former epidemics, at least not in the striking and oft repeated picture of parkinsonism and of the vegetative disturbances associated with it.

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Notes and News

Registry of Lesions of Lymphatic System.—The American Association of Pathologists and Bacteriologists has authorized a registry of lesions of the lymphatic system and has designated the Army Medical Museum as the registrar and the depository of this registry. The same general procedure will be followed as that started by Dr. E. A. Codman in his registry of bone sarcoma under the auspices of the American College of Surgeons. While the primary object is to gain every possible bit of information with regard to Hodgkin's disease and other lesions of the lymphatics, many confusing conditions which result in enlargement of these structures will probably be reported. For the present, all cases of any especial interest are desired, particularly those in which recovery has followed a diagnosis of malignancy, those in which there has been a series of biopsies prior to a subsequent autopsy, and those in which good histories are available. The clinical record should contain at least as much as is usually furnished for necropsy protocols and should include the age, sex, color, social status, results of examination of the blood, the quality and quantity of any type of irradiation, the clinical diagnosis, and roentgen-ray prints which may show the extent of internal masses. The presence or absence of tuberculosis, syphilis, skin or other infections should be noted. Most important are thin, well stained sections. Extra blocks or unstained paraffin sections for special stains and to cover the loss in breakage which occurs in the circulation of this material, will materially add to the value of the case.

The following is a list of conditions and synonyms requested for registration:

Lymphosarcoma	Myelocytic leukemia
Small round cell sarcoma	Chloroma
Lymphoblastoma	Large round cell sarcoma
Lymphoma	Large cell lymphosarcoma
Lymphocytoma	Endothelioma
Pseudoleukemia	Granuloma malignum
Lymphatic leukemia	Hodgkin's disease
Small cell	Hodgkin's disease (sarcomatoid)
Large cell	Hodgkin's sarcoma

Since others than pathologists are invited to contribute to this registry, large numbers of confusion diseases will, of course, be sent in.

A classification sheet will eventually be made to cover these confusion conditions, and suggestions for the form of this sheet are desired. The clinical and pathologic diagnoses are requested for purposes of classification. All those interested in this subject are earnestly requested to contribute their ideas as to the scope of the registry and the method of procedure. The material should be mailed to the Curator, Army Medical Museum, where, after classification by the committee (Drs. Ewing and Mallory), it will be circulated among those of the medical profession who are interested.

Death of Albert Robin.—Albert Robin, professor of pathology and hygiene in Temple University, Philadelphia, has died, at the age of 54 years.

Blood Grouping.—The designation of the blood groups by letters (O, A, B, AB) has been adopted by the United States Army and United States Navy.

University News, Promotions, Resignations and Appointments.—Herman G. Weiskotten, dean and professor of pathology, Syracuse University College of Medicine, has been reappointed health officer of the city of Syracuse.

Sydney A. Smith, professor of forensic medicine in the medical school at Cairo, has been appointed to the chair of forensic medicine in the University of Edinburgh made vacant by the death of Henry Harvey Littlejohn.

Sir Frederick Andrews has become emeritus professor of pathology in the University of London.

Granville A. Bennett has been appointed instructor in pathology in the Harvard Medical School.

A. Calmette, assistant director of the Pasteur Institute in Paris, has been elected a member of the French Academy of Sciences.

Ward H. Cook, assistant professor of pathology at the New York Post-Graduate Medical School and Hospital, has resigned to become director of the laboratories at the Nathan Littauer Hospital, Gloversville, New York. His place at the Post-Graduate has been taken by Nicholas M. Alter, formerly pathologist at the Brooklyn Hospital.

James Henry Dible has been made professor of pathology and bacteriology in the Welsh National School of Medicine.

The Cameron Prize of the University of Edinburgh for important additions to practical therapeutics has been awarded to C. Levaditi of the Pasteur Institute in Paris for his work on the chemotherapy of syphilis and for other contributions to microbiology.

Frank Jodzis has been appointed resident pathologist in the radiological department of the Philadelphia General Hospital in the place of E. S. Clayton, who has resigned.

George R. Minot has been appointed as director of the Thorndike Research Laboratory of the Boston City Hospital in place of Francis W. Peabody, the first director, who died not long ago.

International Convention on Cancer Research.—It is planned to hold an international cancer convention in London next July under the presidency of Sir J. Bland-Sutton. The work of the convention will be presented in a number of different sections, including a pathologic section, of which Lazarus-Barlow is the chairman.

Society of American Bacteriologists.—At the annual meeting in Rochester, New York, Alice C. Evans was elected president for 1928, Ludvig Hektoen, vice-president, J. M. Sherman, secretary-treasurer, and R. E. Buchanan, L. W. Famulener, A. P. Hitchens and W. P. Larson, councilors.

Warthin Anniversary Volume.—Aldred S. Warthin, professor of pathology in the University of Michigan, has been presented with a 715 page volume, entitled "Contributions to Medical Science Dedicated to Aldred Scott Warthin," in recognition of his services as teacher of pathology for thirty-five years. In addition to articles by early colleagues, the volume contains articles from members of each of the thirty-five successive classes that received instruction in pathology from Dr. Warthin. The book also contains a complete Warthin bibliography.

Cancer in Tropical Races.—According to De Vogel, of the Institute for Cancer Research in the Dutch East Indies, the incidence of tumors in the Javanese and Chinese on the east coast of Sumatra is not any less than in the corresponding European groups.

Serologic Conference by League of Nations.—The health committee of the League of Nations will hold a serologic conference in Copenhagen from May to July next. Authors of various tests will discuss and demonstrate their own methods.

Obituary

JAMES HOMER WRIGHT

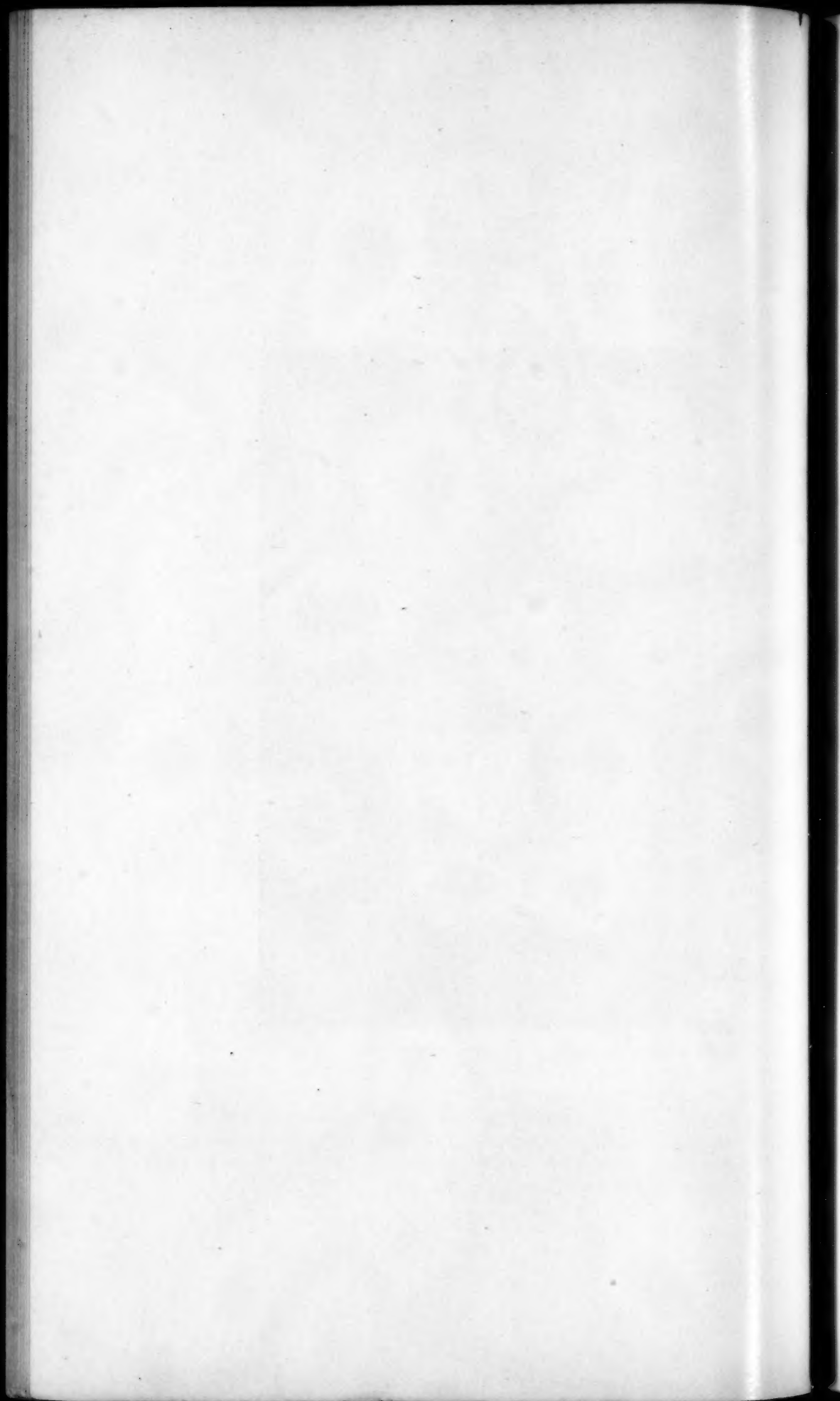
1870-1928

Dr. James Homer Wright, director of the clinicopathologic laboratory of the Massachusetts General Hospital and assistant professor of pathology in Harvard University, died of pneumonia on Jan. 3, 1928, in the fifty-eighth year of his age. He received his A.B. degree from the Johns Hopkins University and his M.D. from the University of Maryland. Harvard University conferred the honorary degree of Sc.D. in 1905.

I first knew Dr. Wright in 1891, when, as a young physician, he came to work in the pathologic laboratory of the Johns Hopkins Hospital, where he was an industrious and painstaking student. The following year he went from there with Dr. A. C. Abbott, University of Pennsylvania, as Scott Fellow in hygiene. His primary work on the bacteriologic examination of the water supply of Philadelphia was undertaken at the suggestion of Dr. J. S. Billings, and a report of it was published by the National Academy of Sciences as a part of the paper of Dr. Billings on the bacteria of river waters. This work of Dr. Wright gave the results of the study of fifty-three types of bacteria, some of them new forms which he found in the water. It was a good, careful piece of work, with nothing particularly original about it, and it might have been done by a student under direction. I speak of this because it was in such striking contrast to his following work. This was all original; he found his problems in the material which came into his hands in the course of work; he was a skilled experimenter and was fertile in devising methods, many of which are in daily use and which have contributed greatly to the increase of knowledge. He never published a report of a method until he had reduced it to the essential details and the description was simple and easily followed. This is particularly true of his method for preparing and using the stain for blood films which, under the name of Wright stain, is in general use. The many methods for work in bacteriology which he described are simple and ingenious. He made a thorough study of photomicrography, and the photographs with which many of his papers were illustrated have never been surpassed. His two most important papers, for both of which he received prizes, were on blood plates and actinomycosis. He was led to the work on blood plates by his interest in thrombus formation and devised methods demonstrating the plates in both the blood and the tissues. He took up the question of their nature, histogenesis and mode of formation, which



JAMES HOMER WRIGHT



up to that time was unknown, and he definitely settled it. Although the process he described was entirely different from other histologic processes in the body, doubt of the accuracy of his judgment was not left in the mind after his demonstration. In actinomycosis he cleared up what was a confused subject, and the culture methods used in its study and in the study of gonococci were valuable contributions to bacteriology. He was the first to demonstrate the presence of syphilitic organisms in the wall of the aorta, thereby proving the relation between syphilis and forms of aortitis, aneurysms and disease of the aortic valves. In the paper on neurocytoma, he described a tumor of the nervous system which had not previously been recognized as such and traced its histogenesis. In 1897, he published with Dr. Mallory the well known and generally used "Pathological Technique" which has reached eight editions.

In the long series of his contributions, I do not think that there is one in which an error in description or in interpretation has been found. The matter is expressed in simple and clear language and without an extraneous word. He had little interest in teaching, though he was a clear and stimulating teacher to the individual student. Essentially an investigator, he avoided as far as possible the routine of the laboratory of the hospital and was able to secure devoted and skilful assistants who relieved him of this.

He was not a social man, rarely going to medical meetings, but he formed many enduring friendships. By his character and his work, he exerted a strong and stimulating influence on the hospital and on the students with whom he came in contact.

W. T. C.

Abstracts from Current Literature

Pathologic Physiology

EFFECT OF ULTRAVIOLET LIGHT ON THE BLOOD OF NEW-BORN INFANTS. H. N. SANFORD, *Am. J. Dis. Child.* **33**:50, 1927.

Studies of fifty new-born infants, normally delivered, twenty-five of whom recieved irradiations begun at the end of the fourth day, showed that short exposure lowered the bleeding time but did not affect the coagulation time and temporarily increased the platelet count. The possibility of using ultra-violet light as a therapeutic agent in infants, with increased bleeding time, is suggested.

RUTH E. TAYLOR.

CONGENITAL LYMPHANGIECTATIC EDEMA. H. O. RUH and L. H. DEMBO, *Am. J. Dis. Child.* **33**:249, 1927.

Detailed necropsy observations of a case of edema of the right side of the neck, tongue, face and head, right upper extremity, left lower extremity and left labia are given. A developmental defect of the mesoderm was thought to be the cause of the anomaly.

RUTH E. TAYLOR.

THE FLUCTUATION IN BLOOD SUGAR DURING ECLAMPSIA AND ITS RELATION TO THE CONVULSIONS. P. TITUS, P. DODDS and E. W. WILLETTTS, *Am. J. Obst. & Gynec.* **14**:89, 1927.

In eclampsia the blood sugar undergoes marked fluctuations, and there is usually a marked drop preceding the convulsion. This drop is considered comparable to an insulin hypoglycemia. Following the convulsion, a temporary rise in the blood sugar occurs. This is considered as the physiologic response of the liver to muscular activity.

A. J. KOBAK.

MICRO-INJECTION STUDIES OF CAPILLARY PERMEABILITY. E. M. LANDIS, *Am. J. Physiol.* **82**:217, 1927.

By the use of a method of micro-injection of dye solutions into single capillaries of the frog's mesentery, the following results were obtained: 1. Dilated capillaries were not more permeable than constricted vessels. 2. The rate of passage of dye solution was dependent on capillary pressure rather than on diameter. 3. With a given pressure, various dyes differed greatly in their rates of passage, depending apparently on their colloidal properties; no basis was found to justify comparison of capillary permeability in this respect with collodion membranes. 4. Vital red HR introduced into the ventricular blood passed at once through the walls of the capillaries in which the pressure was above 14 cm. of water, but was retained for some minutes with pressures below 11 cm. 5. The rate of fluid movement through the capillary wall was proportional to the difference between the capillary pressure and the osmotic tension of the plasma proteins. The latter amounted to 11.5 cm. of water; with capillary pressures in excess of this, filtration took place; below this, there was absorption. 6. Vessels injured by alcohol and mercuric chloride were much more permeable than if they were uninjured.

H. E. EGGERS.

STUDIES OF THE THYROID APPARATUS. F. S. HAMMETT, *Am. J. Physiol.* **82**:250, 1927.

The author ascribes the distortion of differential development which follows the removal of both the thyroid and the parathyroid as due, not to any specific relationship of glandular function to organ growth, but to the general metabolic disturbance so produced. The hypophysis, submaxillaries and possibly the spleen are exceptions to this statement. He regards the differential reaction in other organs as the result of the fact that some organs are more resistant and others more sensitive to the deprivation, as manifested by their growth.

H. E. EGGERS.

THE TRANSPORTATION AND ELIMINATION OF ORGANIC DYES BY THE ANIMAL ORGANISM. M. R. ZIEGLER and L. B. MENDEL, *Am. J. Physiol.* **82**:299, 1927.

Thirty-one dyes were injected into rats, dogs and rabbits to determine what body membranes they could permeate. Of these, twenty-four were eliminated in the urine. Three fat-soluble dyes, yellow AB, yellow OB and oil yellow, were eliminated in water-soluble form in the urine, as a result of conjugation. All except dinitroresorcin and carmine, which are both fat-soluble and water-insoluble, were found in the bile. Three, amaranth, Martius yellow and methyl violet, all of which are water-soluble, but which vary greatly in chemical structure, were found in the pancreatic juice. None was found in the saliva, even after stimulation with pilocarpine or after electrical stimulation of the chorda tympani. Neither dyes nor their leukobases were found in the cerebrospinal fluid. Naphthol yellow S, crystal violet, methyl violet and ethyl violet, stained the mucosa of the gastro-intestinal tract. Of nineteen dyes the presence of which was tested for in the thoracic lymph, all except three appeared there. In the humors of the eye, dyes were not found unless the fluid had been withdrawn and allowed to reaccumulate, in which case five of seven dyes tested were found to have penetrated here. The injection of peptone and histamine as "capillary poisons" did not change the normal excretion of alkali blue and ethyl violet.

While evidently selective secretion or excretion takes place, a constant explanation of this could not be found on the basis of chemical or physical properties. That these may occasionally play a part was indicated in the case of the fat-soluble dyes, the basic members of which were eliminated in the bile and urine, while the acid ones were present in the bile only. The authors suggest that the ability of a dye to conjugate with some other group within the body may play a large part in its elimination.

H. E. EGGERS.

A RACHITIC-LIKE DISTURBANCE IN EXTREME HYPOTHYROIDISM. M. M. KUNDE and A. J. CARLSON, *Am. J. Physiol.* **82**:630, 1927.

In young rabbits, thyroidectomized between two and three weeks after birth, a disturbance in skeletal development was found, showing a fundamental resemblance to that of clinical rickets, accompanied by severe anemia. Control litter mates showed that this condition was not due to dietary deficiency. Blood calcium was normal or only slightly below normal, and acid-soluble phosphorus in the serum was low.

H. E. EGGERS.

EFFECT OF ANOXEMIA ON SIZE OF HEART AS STUDIED BY THE X-RAY. E. J. VAN LIERE, *Am. J. Physiol.* **82**:727, 1927.

In conditions of anoxemia, induced by the use of the respiratory chamber and ranging from 8.3 to 2.5 per cent, dogs, cats, rabbits and guinea-pigs showed

acute cardiac dilatation, as evidenced by roentgen-ray examination. Up to a definite maximum, the degree of this increased with the degree of anoxemia. Much individual variation was observed, some animals showing the change with less oxygen variation than others.

H. E. EGGERS.

UROBILIN PHYSIOLOGY AND PATHOLOGY. P. D. McMASTER and R. ELMAN, *Ann. Int. Med.* 1:68, 1927.

Urobilinuria is an expression of the inability of the liver cells to remove from circulation the urobilin brought by the portal blood stream, with the result that the pigment passes on to the kidney and urine. Urobilinuria occurs with a far less degree of injury to the liver than does bilirubinuria.

The intestinal tract is, under ordinary circumstances, the sole place of origin of urobilin. Urobilinuria, occurring during blood destruction, is primarily the result of an increased excretion of bilirubin, from which, in turn, an unusually large quantity of urobilin is formed within the intestine. The liver fails to remove from the portal blood all of the latter pigment, which is resorbed, and consequently some of it reaches the kidneys and urine.

Evidence could not be adduced to justify the belief that urobilin is ever formed through the action of the parenchyma of the liver. Urobilin appears only when the bilirubin of the bile is reduced by bacteria. Normally this occurs in the intestine, but it may also occur in a biliary tract infected with an appropriate organism. Urobilin in the urine depends, first on the absorption of the substance from the intestinal tract or infected biliary tract, and secondly, on the failure of the liver to remove the pigment from the blood.

WALTER M. SIMPSON.

AN IRRESPONSIVE CONDITION OF THE VESSELS WITH SPECIAL REFERENCE TO THE PATHOLOGY OF TELANGIECTASES AND ALLIED CONDITIONS. T. LEWIS, *Heart* 13:153, 1926.

Following injury to the skin in several ways—by stroking in susceptible persons, and by freezing, burning, mustard gas and mercury vapor lamp irradiation—vascular dilatation and edema are observed. Following the disappearance of the latter, the vessels contract imperfectly or not at all to the stimulus of epinephrine or pituitary extract, and are partially refractory to the stimulus of histamine. A similar observation was made in a case of erythema ab igne, reported here; and in a number of cases of telangiectasis, some from known injuries, some of unknown origin, the vessels showed the same lack of responsiveness to the stimulants mentioned. The writer deduces that the telangiectases owe their origin to a loss of contractile power of the vessels, and that this condition is similar to that of vessels immediately after injury. Even the vessels of the normal skin of the face may lose in part their contractile power, and thereby modify in extent and depth the phenomenon of blushing.

H. E. EGGERS.

ANNULAR EDEMA OF THE SKIN IN A CASE OF INFECTIVE ENDOCARDITIS. T. LEWIS and Y. ZOTTERMAN, *Heart* 13:193, 1926.

A case of infective endocarditis is reported, in which the skin lesion assumed the form of localized edema, with only slight vascular dilatation. The rate of

formation of the edema was slow, presumably for this reason, and in course of time spread marginally, with subsidence at the center.

This course of behavior the writers explain on the basis of a local central intoxication, with radial spread from the center. From previous observations, they believe the agent actually producing the edema to be of histamine-like character. With such substances they have uniformly observed a subsequent refractory state of the vessels, in which these substances do not any longer produce their first effect. With the development of this phase, the central vessels would lose their increased permeability, and the edema would then disappear. Farther support for this theory is furnished by the behavior of the lesions when two of them expand to the point of meeting. In such a case farther progress was arrested, in terms of the theory, because farther progress would have to be over ground already in the refractory state.

This case furnished evidence that the refractoriness to histamine, and insensitiveness to epinephrine, while commonly associated, are not necessarily of similar origin, since the former was present, the latter absent.

H. E. EGGERS.

SOME EFFECTS OF ULTRA-VIOLET LIGHT. T. LEWIS and Y. ZOTTERMAN, *Heart* 13:203, 1926.

The effect of ultraviolet light on the skin was found to be a local active vasodilatation, with a slight reflex dilatation of the muscular arterioles, and a locally increased permeability of the vessel walls.

The vasodilator substances formed by the action of the light diffuse into the surrounding areas and are carried away by the lymphatic channels; these substances are believed to be of histamine-like character, as with injuries from other causes. The latency of the light burns, they believe, is due to a liberation of these substances much more gradually and continuously than in the case of injuries by other causes.

H. E. EGGERS.

NOTES ON THE ANAPHYLACTIC SKIN REACTION. T. LEWIS and R. T. GRANT, *Heart* 13:219, 1926.

The report concerns a case of urticaria, in which the subject was hypersensitive to fish or fish extracts. There was not any abnormal susceptibility to histamine or to mechanical injury. The anaphylactic reaction obtained here resembled exactly that following various kinds of injury, including histamine injection. The fish substance responsible appeared to be associated chiefly with nucleic acid, and was about 170 times as active in this subject as histamine; the reaction is explained by the liberation by the anaphylactic poison, from the skin of a histamine-like substance.

H. E. EGGERS.

MENSTRUATION AND OVULATION IN MONKEY: POSSIBLE SIGNIFICANCE FOR MAN.

G. W. CORNER, *J. A. M. A.* 89:1838, 1927.

In young mature females of the monkey (*Pithecius [Macacus] rhesus*), menstruation frequently occurs without ovulation, and is therefore not dependent on the presence of a corpus luteum. However, when ovulation occurs, it seems to take place at a definite time, about twelve or fourteen days before the onset of menstruation. Menstruation without ovulation is not preceded by the

so-called premenstrual changes of the endometrium, which occur only after formation of the corpus luteum. The cause and meaning of menstruation, in this species, are not at present known. Physicians in a position to obtain human material are urged to gather and study it in the light of these new facts discovered in a related species.

AUTHOR'S SUMMARY.

POLYGLOBULIA INDUCED BY CEREBRAL LESIONS. KAMIL SCHULHOF and MABEL M. MATTHIES, J. A. M. A. **89**:2093, 1927.

Polyglobulia of long duration induced by a lesion of the proximal part of the vegetative centers of the brain in rabbits indicates that the brain plays a rôle in the regulation of the number of circulating erythrocytes. This conclusion is supported by the polyglobulia observed in some cases of epidemic encephalitis.

METABOLISM IN SCLERODERMA. WARFIELD T. LONGCOPE, J. A. M. A. **90**:1, 1928.

In a case of generalized scleroderma with deep pigmentation, attacks of mental confusion and delirium occurred repeatedly after short periods of fasting. These attacks were associated with hypoglycemia. The resemblance between many of the symptoms in this case and those occurring in some instances of Addison's disease was noteworthy.

In a study of five other cases of generalized scleroderma, the blood sugar, as well as the other chemical constituents of the blood, did not deviate materially from the normal.

In three cases the basal metabolic rate tended to fall below normal, and the administration of thyroid extract in these cases was attended by symptomatic improvement.

In one fatal instance of acute and extensive scleroderma in a young man, autopsy disclosed atrophy of one suprarenal gland and interstitial orchitis.

It is possible that disturbances in the function of the glands of internal secretion, which occasionally accompany scleroderma, may in some instances occur as a result of involvement of these organs by the generalized process, and thus do not have a direct bearing on the etiology of scleroderma.

AUTHOR'S SUMMARY.

THE BLOOD LIPOIDS IN EXPERIMENTAL DIABETES. W. R. BLOOR, E. M. GILLETTE and M. S. JAMES, J. Biol. Chem. **75**:61, 1927.

Severe diabetes is frequently characterized by a slight hyperlipemia which appears to be independent of the amount of food fat ingested and which is secondary to the disturbance in carbohydrate metabolism. The lipemia may be due to a diminished responsiveness in the fat-removal mechanism such as would require the stimulus of an abnormally high blood fat concentration for effective operation.

ARTHUR LOCKE.

THE COMPOSITION AND RESPIRATORY EXCHANGES OF HUMAN BLOOD IN TERMINAL CHRONIC NEPHRITIS. L. J. HENDERSON, A. V. BOCK, D. B. DILL, L. M. HURXTHAL and C. VAN CAULAERT, J. Biol. Chem. **75**:305, 1927.

This paper consists of a monographic description of the changes in the blood and respiration in chronic nephritis at the point of death.

AUTHORS' SUMMARY.

IS THERE A TRAUMATIC DIABETES? F. UMBER and M. ROSENBERG, *Klin. Wchnschr.* 6:5, 1927.

Based on eight cases, the conclusion is drawn that true traumatic diabetes does not exist. Often an extra-insular glycosuria is mistaken for diabetes.

J. D. WILLEMS.

THE INFLUENCE OF LOCAL APPLICATION OF INSULIN ON THE REGENERATIVE ACTIVITY OF THE SKIN. D. ADLERSBERG and A. PERUTZ, *Klin. Wchnschr.* 6:108, 1927.

Insulin, when applied locally, increased the cell activity of the skin so that chronic ulcers, which had resisted all treatment for a long time, healed quickly.

J. D. WILLEMS.

WATER METABOLISM AND THE QUENCHING OF THIRST. E. STARKENSTEIN, *Klin. Wchnschr.* 6:147, 1927.

Extensive experiments show that distilled water is excreted by the kidneys shortly after it is drunk. Isotonic salt solutions and acidified solutions are retained if absorbed by the intestine; they may be nonabsorbable and act as laxatives. So-called soda water increases the excretory action of the skin. The optimum for retention is a slightly acidified, half isotonic solution of sodium chloride.

J. D. WILLEMS.

EXPERIMENTS ON OPERATIVE TREATMENT OF DIABETES. G. MANSFELD, *Klin. Wchnschr.* 6:195, 1927.

When the pancreas of a dog is completely ligated at its middle, without injury to the blood vessels, change does not take place in the proximal part, while in the ligated part there is histologically an increase in the number of islets. The blood sugar level of the dog is lowered and the sugar tolerance markedly increased, owing to overproduction of insulin in the ligated part of the pancreas. The application of this principle to the treatment of juvenile diabetes is considered.

J. D. WILLEMS.

CHOLESTEROL METABOLISM. H. BEUMER, *Klin. Wchnschr.* 6:1749, 1927.

Exogenous cholesterol is eliminated quantitatively by the liver.

E. F. HIRSCH.

GROWTH STIMULATING EFFECT OF LACTIC ACID. H. VOLLMER, *Klin. Wchnschr.* 6:1806, 1927.

Rats that were fed lactic acid increased in weight more rapidly than controls.

E. F. HIRSCH.

FEMALE SEX HORMONE IN THE URINE OF MEN. ERNST LAQUEUR, E. DINGEMANSE, P. C. HART and S. E. DE JONGH, *Klin. Wchnschr.* 6:1859, 1927.

A substance having the characteristics of the female sex hormone was found in the urine of men.

E. F. HIRSCH.

DOES THE INTERNAL SECRETION OF THE PANCREAS FUNCTION IN FAT RESORPTION? H. LICHT and A. WAGNER, *Klin. Wchnschr.* 6:1982, 1927.

Recent reports do not conclusively dispose of the possibility of a resorption of food favoring internal secretion of the pancreas. The influence of insulin on resorption of food was studied (a) in patients with pancreatic disease and marked disturbances in resorption and (b) in depancreatized dogs. Doses of insulin sufficient to prevent pathologic carbohydrate disturbances did not have any effect on the resorption of food. Ligation of the pancreatic ducts leads to severe disturbances in resorption as does extirpation of the pancreas. These results lead to the conclusion that the pancreas does not furnish a resorption of food favoring internal secretion.

AUTHORS' SUMMARY.

IS DEXTROSE A HORMONE FOR INSULIN SECRETION? E. GEIGER, *Klin. Wchnschr.* 6:2000, 1927.

The contention of Grafe and Meythaler that dextrose stimulates the islet tissues is not confirmed. The solutions injected into the pancreatic artery may cause hypoglycemia because of their high osmotic concentration and not because of their sugar concentration.

AUTHOR'S SUMMARY.

RELATION BETWEEN HYPOPHYSIS AND GENITAL ORGANS. L. D. PODLJASCHUK, *Strahlentherapie* 24:439, 1927.

This article in an intended series deals with the relation between the hypophysis and the genital organs. Eight rabbits and five dogs were treated over the right and left temporal and frontal regions. In the first group, three of five rabbits (ten weeks old) received approximately 25 per cent, 35 per cent and 45 per cent erythema doses to the hypophysis; the two remaining animals served as controls (3 aluminum, 25 cm. focal skin distance, quality of radiation 11 to 12 Wehnelt; this would correspond to a half value layer of from 1.2 to 1.4 cm. of water). After from sixty to seventy-four days, all five animals were killed. There was not any appreciable change in the gained weight; macroscopic changes could not be noticed in any organ. Section of the hypophysis showed more eosinophils than normal; the individual cells seemed larger. No stimulating effect of small doses of roentgen rays may be deduced from this result.

In the second group, two of three rabbits (7 months old) were exposed to 130 per cent erythema doses effective in the hypophysis (180 kilovolts, 4 milliamperes, 0.5 copper plus 1 aluminum, 23 cm. focal skin distance, 2 by 5 cm. field, over the temples and 4 by 6 cm. field over the frontal, one erythema surface dose per field). After seventy-two days all three rabbits were killed; one treated animal had lost in weight. Histologic section of the hypophysis showed degeneration and atrophy. Changes in the genital organs were not noticed.

The third group consists of five dogs (8 weeks old) that received from 75 per cent to 130 per cent erythema doses effective in the hypophysis, of the same radiation as used in group 2. The heavily treated dogs were killed after fifty-eight and seventy-two days; the other and the control died after seventy-six days. The cause of death was undetermined. As a result of the treatment, the growth and development appeared delayed. The genital organs were atrophied. There seems to be a great difference between the reaction of adult

and young growing animals following roentgen-ray irradiation of the hypophysis. The relation between genital organs and the pituitary gland requires further investigation.

E. A. POHLE.

THE EFFECT OF ROENTGEN RAYS ON UNICELLULAR ORGANISMS. G. H. KLÖVE-KORN and P. GAERTNER, *Strahlentherapie* **24**:548, 1927.

In this second series of experiments a number of unicellular organisms were exposed to radiation of lambda effective at 1.47. The erythema dose is 380 R (70 kilovolts, 9 milliamperes, 7.5 cm. distance, no filter). It required 767 erythema doses, ten minutes, to kill *Trichophyton crateriforme*; 767 erythema doses, ten minutes, to kill *Trichophyton umbilicatum*; 767 erythema doses, ten minutes, to kill *Achorion quinckeanum*. Fresh water amebas were treated for forty-five minutes with 3,450 erythema doses equal to 1,312,000 R. A definite retardation of their movements could be observed. Increasing the time to seventy-five minutes (5,750 erythema doses or 2,190,000 R) showed the same effect as before, only in a higher degree. None of the amebas were killed.

E. A. POHLE.

THE BIOLOGIC EFFECT OF ROENTGEN RAYS AND ITS INVESTIGATION WITH THE EXPLANATION METHOD. M. SCHUBERT, *Strahlentherapie* **24**:551, 1927.

Krontowski has recently demonstrated that roentgen ray doses that are fatal for a chicken embryo do not stop, for instance, the growth of a heart tissue culture explanted after the exposure. Schubert repeated these experiments and came to the same conclusions. He found, however, that if two hours have passed since the irradiation, before the culture is started, the first signs of injury are evident in it; after an interval of three hours growth could not be obtained. Normal heart tissue cultures placed in extract taken from frozen or irradiated eggs, three hours after either procedure, developed almost normally, while in the case of a twenty-four hour interval, definite retarding of growth resulted. The extracts from the frozen or irradiated eggs had a higher hydrogen ion concentration than normal. As lethal dose for chick embryos in ovum, 10 erythema doses (60 kilovolts, 20 cm. distance, no filter, 1 erythema dose equals two and one-half minutes) were chosen.

E. A. POHLE.

BASAL METABOLISM IN ACUTE ALCOHOLISM. A. KAUKEPP, *Folia Neuro-pathologica Estoniana* **7**:110, 1917.

When rabbits were given 2 cc. of 96 per cent alcohol, the basal metabolism was from 6 to 26 per cent above normal. When they were given 3 cc. of alcohol, the rate was increased from 18 to 53 per cent.

ROY GRINKER.

Pathologic Anatomy

CONGENITAL DEFECT IN THE MUSCULATURE OF THE ABDOMINAL WALL. K. IKEDA and A. V. STOESE, *Am. J. Dis. Child.* **33**:286, 1927.

A case is described in which the entire anterior abdominal wall was absent and the urinary bladder greatly enlarged. A review of the literature of similar cases is given and the suggestion made that the changes in the urinary system in these cases are secondary to the anomalous condition of the abdominal wall.

RUTH E. TAYLOR.

THE ORIGIN OF THE COMMON CYSTIC STRUCTURES OF THE HUMAN PLACENTA.
R. PADDOCK and E. D. GREER, *Am. J. Obst. & Gynec.* **13**:164, 1927.

From a study of a large number of placentas, Paddock and Greer conclude that the so-called decidual islands are maternal in origin, and are portions of the decidual septums. The cystic structures, seen in 14.1 per cent of their series, are the result of action of trophoblastic tissue on the decidual islands. The Langhans cells particularly play a part in producing cystic changes, which are frequently associated with white infarction.

A. J. KOBAK.

TRANSPLANTATION AND INDIVIDUALITY DIFFERENTIALS IN INBRED FAMILIES OF GUINEA-PIGS. LEO LOEB and SEWALL WRIGHT, *Am. J. Path.* **3**:251, 1927.

In the former series of investigations of Leo Loeb, it has been shown that the intensity of the reactions appearing after transplantation furnished a quantitative measure of the similarity or difference between individuality differentials. It was to be assumed that through long continued inbreeding the individuality differentials among the members of the inbred family would gradually become more and more alike. Under these conditions it was of interest to extend these experiments to inbred strains, and this paper deals with the results obtained in the exchange of tissues in families of guinea-pigs which have been inbred in the United States Department of Agriculture since 1909. The aim of this series, therefore, is similar to that of the preceding one in which transplantations were carried out in strains of inbred rats, but the results differ in both series. It may be concluded that within the inbred families of guinea-pigs the individuality differentials have reached a great similarity, and that the resemblance of the individuality differentials among members of an inbred family which are not closely related is much greater than that among brothers in noninbred families. There is, however, not yet an identity of the individuality differentials. A complete loss of individuality has not yet been reached within the inbred families. On the whole, brothers and sisters seem to have reached identity of individuality after from nineteen to twenty generations of continuous brother and sister matings; at least no reaction was elicited in the host on the part of the transplant within the range of time used in our experiments. In a few cases, however, a lack of complete identity was observed even under these conditions. Transplantations from hybrids to mother or father strains and the reciprocal transplantations have shown that it is the number of strange genes (and perhaps also the intensity of the strangeness of the composing genes) in the individuality differential of the transplanted tissue which determines the severity of the reaction of the host against the transplant. The presence of strange genes in the individuality differential of the host, the absence of certain genes in the transplant or the presence of double genes in the transplant does not call forth a reaction in the host. As in transplantations between individuals of noninbred families, toxins developing as the result of incompatibility of individuality differentials influence the lymphocytic and connective tissue reactions, and the behavior of the blood vessels may cause the direct degeneration of sensitive tissues.

LEO LOEB.

OSTEOSCLEROTIC ANEMIA SECONDARY TO EPIDERMOID CARCINOMA. G. Y. RUSK and W. L. MILES, *Am. J. Path.* **3**:289, 1927.

The primary carcinoma arose in the skin over the region of the left molar region. A peculiar anemia developed which is ascribed to widespread replacement of marrow by metastatic growths.

PULMONARY BLASTOMYCOSIS; ITS SIMILARITY TO TUBERCULOSIS. E. M. MEDLAR, *Am. J. Path.* **3**:305, 1927.

The similarity of the changes in the lungs in two cases of blastomycosis to those in pulmonary tuberculosis is emphasized.

SIMILARITY OF RETICULUM IN LUNG IN BLASTOMYCOSIS AND TUBERCULOSIS. W. SNOW MILLER, *Am. J. Path.* **3**:315, 1927.

The growth and transformation of reticulum into collagenous tissue appear to be identical in blastomycosis and tuberculosis of the lungs.

MULTIPLE HEMORRHAGIC CUTANEOUS SARCOMA OF KAPOSÍ. D. S. MEYERS and V. C. JACOBSON, *Am. J. Path.* **3**:321, 1927.

A case in a man, aged 82, is described. The histogenesis is traced to a multiple hemangiomatosis with fibromyomatous change in the stroma.

THE GLOMERULUS IN EXPERIMENTAL HYPERTROPHY OF THE KIDNEYS OF RABBITS. OTTO SAPHIR, *Am. J. Path.* **3**:329, 1927.

In hypertrophic kidneys most of the glomeruli are enlarged, but there is no increase in their number. After removal of one kidney, there is first hyperemia and later cloudy swelling of the remaining kidney, which reaches its acme in about three weeks, and then disappears.

SYMPATHICOTROPIC CELLS OF OVARY AND TESTIS. DORSEY BRANNAN, *Am. J. Path.* **3**:343, 1927.

It is recommended that the term "sympathicotropic" (Berger) be applied to certain epithelial cells in the hilum of the ovary and testis because of their close association with nonmedullated nerves. These cells are not constant. They have nothing to do with suprarenal rests, and their function is unknown. They may increase in number and size during pregnancy.

SYNOVIOMATA. LAURENCE W. SMITH, *Am. J. Path.* **3**:355, 1927.

Three instances of synoviomata are described. Such tumors may arise from the synovial membrane of joints and bursae, from fascial aponeurosis, and from tendons and tendon sheaths. Histogenetically, they are traced to mesothelial cells with multipotential characteristics. The literature is reviewed.

CYTOLOGIC STUDY OF MOLLUSCUM CONTAGIOSUM. ERNEST W. GOODPASTURE and HOWARD KING, *Am. J. Path.* **3**:385, 1927.

The observation by Lipschütz that epithelial cells in the lesions of molluscum contagiosum contain myriads of minute bodies morphologically consistent with a filter-passing organism has been confirmed. These bodies are not derived from extruded nucleoli, nor from any formed cytoplasmic constituent. The bodies develop about, and later within, cytoplasmic vacuoles, which may be regarded as the cellular response to the presence of a living foreign body. The view is expressed that these bodies may be the virus and the etiologic agent of molluscum contagiosum.

AUTHORS' SUMMARY.

NUCLEAR CHANGES OF GANGLION CELLS IN EXPERIMENTAL HERPETIC ENCEPHALITIS. ERNEST W. GOODPASTURE, *Am. J. Path.* **3**:395, 1927.

Intranuclear bodies, distinct from herpetic inclusions, may occur within ganglion cells in acute herpetic encephalitis. These bodies may consist of myelin and have morphologic relation to the specific virus.

CHANGES IN THE OVARY OF THE MOUSE FOLLOWING EXPOSURE TO X-RAYS:
PART 2. IRRADIATION AT OR BEFORE BIRTH. F. W. R. BRAMBELL, A. S.
PARKES and UNA FIELDING, *Proc. Roy. Soc., London* **101:29**, 1927.

The roentgenograms of ovaries of six mice in utero and thirty at birth are described. The observations were similar to those in roentgenograms of animals taken at 3 weeks (reported in a previous communication), and showed degeneration of the oocytes and follicles, to be followed by two proliferations of the germinal epithelium in the form of cords. Some of the animals irradiated at birth were allowed to grow to the adult stage, and then the ovaries were studied. These were divided into three groups based on the histologic appearance of the proliferating cords. The authors conclude that the first proliferation of the epithelial cords is responsible for the production of estrum. When this proliferation becomes differentiated into luteal-like cells, estrum is inhibited.

A. J. KOBAK.

ETIOLOGY OF ENDEMIC GOITER. M. MESSERLI and E. COULAUD, *Ann. de l'Inst. Pasteur* **40:952**, 1926.

A study of the thyroids of white rats in Paris where human beings are comparatively free from goiter, in Lausanne and Strasbourg where goiter is moderately endemic, and in Zurich, a region of pronounced goiter development, reveals a close parallelism in the size, weight and histologic structure of the thyroids of rats and of men. In localities in which goiter is endemic the thymus as well as the thyroid in rats is enlarged, and it is suggested that the diversity of opinion concerning the persistence of the thymus in man may be the result of observations in different regions where goiter may or may not be endemic.

G. B. RHODES.

RETICULUM OF BONE MARROW. F. ORSÓS, *Beitr. z. path. Anat. u. z. allg. Path.* **76:36**, 1926.

In this study the reticulum of bone marrow is compared with that of lymphoid tissue, previously reported by the same author (*abstr. ARCH. PATH.* **2:933** [Dec.] 1926). In both tissues the reticulum is primarily intracellular in origin, being laid down in the bone marrow within reticulum cells which are united by their branching processes to form a syncytium. In the marrow, the reticulum is less well developed and forms a less complete network than in the lymphoid tissues. It is therefore a less resistant and more labile structure. The blood sinuses of the marrow do not have any connective tissue walls, but only an endothelial lining, which is incomplete in the red marrow. A few reticulum fibrils support the sinus walls. In the fatty marrow the sinus walls are complete and the sinuses form a complete system. The reticulum surrounds the fat cells in basket fashion. In conditions associated with long-standing passive congestion the reticulum is increased, but the sinuses remain open. In purulent osteomyelitis the reticulum is disrupted, but as the duration of the process is prolonged the reticulum increases and becomes sclerotic, often forming a complete fibrous wall about the sinuses.

O. T. SCHULTZ.

COMPLETE ABSENCE OF ONE LUNG. F. DANNHEISSER, *Beitr. z. path. Anat. u. z. allg. Path.* **76:87**, 1926.

The rare anomaly reported by the author occurred in a man, aged 34 years, who died as the result of a fracture of the skull. External maldevelopments were not present, and the chest was symmetrical. No vestige of the left lung

could be found. The large, single, three lobed right lung extended far over to the left and covered the heart, which was situated to the left of the mid-line, the apex lying against the left chest wall. The trachea was normal and divided at the usual situation into two main bronchi, both of which entered the right lung. Injection made into the bronchi demonstrated the presence of two complete bronchial trees within the lung. There was only a single pulmonary artery and pulmonary vein. The various theories that have been proposed to explain the absence of a lung are briefly discussed, the author accepting a failure of development, of the *Hemmungsbildung* type, as the most probable explanation. The presence of a double bronchial tree in the single lung of his patient is accepted as evidence that the original single pulmonary anlage failed to undergo division into two lungs.

O. T. SCHULTZ.

CONGENITAL ELEPHANTIASIS. H. WILLI, Beitr. z. path. Anat. u. z. allg. Path. **76**:98, 1926.

A male child, who died at the age of 6 days, presented a greatly enlarged right lower extremity at birth. On microscopic examination the markedly thickened subcutaneous tissue was found to contain numerous widely dilated lymphatics, many of which were cystic. Cellular proliferative reactions were not present in the surrounding tissues. The lymphatics of the brain and spinal cord were ectatic, and dilated lymphatics were present in the leptomeninges. The condition is explained as maldevelopment of the hamartoma type, which consisted in an excess development of lymphatics.

O. T. SCHULTZ.

FORMATION OF ADIPOSE TISSUE IN THE PLEURA. M. BRANDT, Beitr. z. path. Anat. u. z. allg. Pathol. **76**:133, 1926.

True fat cells occur only sparsely in the pleura. In the thickened, chronically inflamed pleura, both visceral and parietal, an abnormal amount of adipose tissue may be present; in one of the cases studied it stimulated a lipoma. The formation of this tissue is held to be the result of the deposition of fat in the proliferated mesenchymal elements and lymphatic stasis in the thickened pleura, with consequent poor nutrition of the tissues as the underlying factor.

O. T. SCHULTZ.

EFFECT OF LOWERED ATMOSPHERIC PRESSURE. A. ROSIN, Beitr. z. path. Anat. u. z. allg. Path. **76**:153, 1926.

The effect of reduced atmospheric pressure and of decreased oxygen content of the respired air with normal atmospheric pressure was studied in guinea-pigs and mice. The latter were found to be much the more resistant of the two species used. Guinea-pigs showed marked alterations after forty hours, consisting chiefly of fatty change in the myocardium, renal epithelium and liver. The spleen contained nucleated erythrocytes, and the lungs were hyperemic. In the mice only slight fatty change occurred in the liver. Nucleated red cells were present in the spleen, and the lungs were congested. The hydrogen ion concentration of the tissues was unchanged.

O. T. SCHULTZ.

CHOLESTEROLEMIA, XANTHOMATOSIS AND FAMILIAL CHOLELITHIASIS. A. RANZEL, Deutsche med. Wchnschr. **73**:2119, 1926.

In addition to attacks of gallstones, the patient had xanthomas and increase in blood cholesterol (up to 0.812 per cent). The gallstones contained 96 per cent of cholesterol. Her mother and three sisters also had gallstones.

A NEW EXPERIMENTAL FORM OF TOXIC LIVER DAMAGE WITH TECHNICAL CHLORANIL OF CHLORANIL BY-PRODUCT. H. STAUB, Frankfurt Ztschr. f. Path. **35:124**, 1927.

In technical chloranil there is a substance which electively destroys the liver of rabbits when administered orally. A sufficient dose (from 5 to 10 Gm. in 100 cc. of water, for rabbits weighing from 2 to 3 Kg.) causes death in from six to ten days due to liver insufficiency.

Grossly, the liver is enormously enlarged to from three to four times the normal weight chiefly due to absorption of water. The surface of the liver is pale brown with many yellow-white necroses and hemorrhages. The tissue is friable and easily torn. Microscopically, in the early phase of the poisoning, there is clearing of the protoplasm and fading of the nuclei of liver cells about the centers of the lobules. The cells in the peripheries show swelling. In the second phase the peripheral cells become swollen and vesicular and irregular necroses are dispersed through the liver tissue. The development of the "bile-ducts" is greatly increased so that scarcely any indication of the normal liver structure remains. The kidneys show only swelling of the epithelium is convoluted tubules.

E. M. HALL.

UNDIFFERENTIATED BLOOD CELLS AND MESENCHYMAL RESTS IN THE ADULT ORGANISM. A. MAXIMOW, Klin. Wchnschr. **5:2193**, 1926.

Maximow reviews critically the unitarian and dualistic theories of the origin of the blood and loose connective tissue cells. The earlier descriptive work has failed to decide definitely between the two theories. The more recent experimental work, particularly with tissue cultures, is summarized, and it is shown from this that in lymph gland cultures lymphocytes may develop into plasma cells, and macrophages (polyblasts). In cultures of blood, lymphocytes and monocytes form macrophages, fibroblast-like cells, and in the presence of tubercle bacilli, epithelioid cells. Monocytes can be shown to arise from lymphocytes. In experimental heterotopic marrow formation, the intravascular lymphocytes form the first myelocytes and erythroblasts. Lymph gland culture with marrow extract showed formation of myelocytes from the lymphoblasts of the germinal centers. Thus, it is shown that the large lymphocyte, of which the small lymphocyte is a proliferation product suitable for transportation in the blood stream, is a general stem cell (hemocytoblast) for all the blood cells and connective tissue wandering cells.

Evidence also exists that this stem cell may, in its turn, be derived from fixed tissue elements—as reticulum cells in lymph nodes. Maximow denies the hemopoietic potentialities of the fibroblast and of the vascular endothelium cell in the adult, showing that the latter furnishes only capillary buds in culture. The true source of inflammatory wandering cells is rather the adventitial cells, and a layer of cells between these and the endothelium, the so-called pericytes. The Kupffer cells in the liver and the splenic reticulum cell are of these classes and may furnish lymphocytes, macrophages and epithelioid cells. The formation of red cells and granular leukocytes from adventitial cells has not been confirmed in tissue culture work.

R. D. LILLIE.

A CASE OF STRANGULATED PULMONARY HERNIA. KOENNECKE, Klin. Wchnschr. 6:73, 1927.

A man, aged 39, had a fist-sized, reducible swelling above the left clavicle for several years. When it became irreducible, operation disclosed a herniation of the lung between the sternocleidomastoid and the scalenus anterior muscles.

J. D. WILLEMS.

ERYTHROCYTOSIS IN ACROMEGALY. J. NEUBURGER, Klin. Wchnschr. 6:168, 1927.

The erythrocyte count in a patient with acromegaly ran parallel with the course of the disease, rising from normal to a high point of 6,500,000, and falling as the condition subsided under treatment.

J. D. WILLEMS.

LONGITUDINAL FRACTURE OF A RIB AFTER COUGHING. H. SCHOENEMANN, Klin. Wchnschr. 6:262, 1927.

A woman, aged 44, after severe cough in the later stages of tuberculosis, developed pain in the region of the left eleventh rib. At autopsy a longitudinal fracture was found.

J. D. WILLEMS.

PATHOLOGY OF BRONCHIAL ASTHMA. W. DEHNER, Klin. Wchnschr. 6:1412, 1927

Two cases of genuine bronchial asthma in which death occurred in asthmatic attacks from asphyxiation are described clinically and anatomically. In one case, there was marked secretion of mucus in the bronchi of middle size, and it is suggested that in certain cases the asthmatic attack may be associated with increased secretion of bronchial mucus. The eosinophils appeared to migrate into the bronchial wall during the asthmatic attack. In both the cases, there was hypertrophy of the right side of the heart and increase in the thickness of the pulmonary arteries of middle size.

THE HISTOLOGIC DEMONSTRATION OF LIPOIDS IN WHITE BLOOD CELLS AND THEIR RELATION TO THE OXYDASE REACTION. E. SEHRT, München. med. Wchnschr. 74:139, 1927.

By a new method, blood smears are stained with sudan III demonstrating the presence of lipoid granules in the neutrophil, eosinophil, mononuclear and transitional leukocytes. The form of the granules and their distribution within the cell body correspond closely with the form and distribution of oxydase granules.

J. D. WILLEMS.

CHANGES IN THE SELLA TURCICA IN CEREBRAL TUMORS. H. HARMS, München. med. Wchnschr. 74:274, 1927.

In a woman, aged 49, there were choked optic disks, increased pressure and protein content of the cerebrospinal fluid, and roentgenologic changes of the sella turcica with absence of hemianopia and of disturbances of the internal secretory gland. The diagnosis of cerebral tumor was substantiated at autopsy by finding a tumor of the right temporal lobe.

J. D. WILLEMS.

CONGENITAL ENCAPSULATION OF THE SMALL INTESTINE. R. FÜTH, München. med. Wchnschr. 74:319, 1927.

A girl, aged 15, had intestinal obstruction with intermittent attacks of acute pain and a constant abdominal mass. The diagnosis made was ovarian cyst on

a twisted pedicle. Operatively a large encapsulated mass was removed which proved to be a peritoneal sac containing more than three fourths of the closely coiled small intestine which consisted only of mucus and muscular coats.

J. D. WILLEMS.

INFARCT-LIKE AREAS IN THE KIDNEYS OF TUBERCULOUS INDIVIDUALS. K. SPRING, *Virchows Arch. f. path. Anat.* **261**:649, 1926.

Spring made a histologic study of areas resembling recent or healed infarcts in the kidneys of persons with tuberculosis. Orth and his pupils had ascribed such lesions to changes in the distribution of an artery occluded by tuberculous periarteritis. Spring recognizes three types of lesion; small, pale streaklike or wedge-shaped areas, with the base at the surface and the apex at the corticomedullary junction; larger, slightly depressed, grayish or grayish red scars, similar to those seen in the arteriosclerotic kidney and wedge-shaped, pale lesions whose surface is covered with miliary tubercles, or which are recognized as caseous infarcts. The first type may be an excretory tuberculosis limited to a cortical unit, or it may be nonspecific in character and the result of localized circulatory disturbance within the cortex of the kidney as may occur in heart failure, in edema of the kidney or following agonal embolism of small vessels. The depressed scars are sometimes the result of nonspecific arteriosclerotic thickening; at other times they are due to partial or complete organization of areas in which the arteries have been not entirely occluded by tuberculous periarteritis or endarteritis. His third type of lesion, the tuberculous character of which is evident in the gross, is the result of the distribution of tubercle bacilli within an area supplied by a terminal artery.

O. T. SCHULTZ.

FATTY REPLACEMENT OF THE PANCREAS. J. KNOFLACH, *Virchows Arch. f. path. Anat.* **261**:666, 1926.

In the three cases reported by Knoflach, the head of the pancreas, which retained its normal gross structure, was distinct from the rest of the organ, which had been replaced by adipose tissue and had undergone a condition of adipose pseudohypertrophy. In one case a calcified cyst and in another an area of dense fibrosis was present at the junction of the normal and fatty portions, whereas, in the third case thickened ducts of the fatty portion were filled with concretions. The acinar tissue had disappeared completely and had been replaced by adipose tissue in which normal islands were scattered. None of the patients had had sugar in the urine. According to the author, adipose replacement of a large part of the pancreas with preservation of its internal secretory function can occur as the result of a necrotizing, obstructive or inflammatory lesion which destroys the pancreatic tissue slowly enough to permit the body to accommodate itself to the loss of tissue.

O. T. SCHULTZ.

FIBRINOUS CALCULI OF THE RENAL PELVIS. W. FLOTTMANN, *Virchows Arch. f. path. Anat.* **261**:685, 1926.

In a woman, aged 39, with pyuria and a history of renal colic and with the roentgenographic observations of a stone in the pelvis of the kidney, the latter organ on operative removal was found transformed into a pus-filled sac. In the dilated pelvis were twelve irregularly rounded, rather soft, laminated concretions. On microscopic examination the latter were composed

of albuminous material which gave the staining reaction of fibrin. The small number of previously reported renal calculi of similar composition is reviewed. While admitting the formation of such masses as the result of hemorrhage into the pelvis of the kidney, the author thinks it more probable that they arise from precipitated colloids excreted by damaged renal tubules.

O. T. SCHULTZ.

PAGET'S DISEASE OF THE NIPPLE. W. ARND, *Virchows Arch. f. path. Anat.* **261:700**, 1926.

After a brief review of the literature, chiefly continental European, the author describes in detail the results of his microscopic examination of three cases of Paget's disease. In one case there was an associated carcinomatous nodule in the mammary body and in another case carcinomatous changes were present in the mamillary ducts. The process present in the epidermis, as described by the author, consisted of moderate thickening of the epidermis, with ulceration in only one case; irregularity of the malpighian layer and the presence within the epidermis, singly and in groups, of the characteristic large, pale, often vacuolated cells, originally described by Paget. These cells gave a marked glycogen reaction. Isolated Paget cells were present in the hair follicles, sebaceous and sweat glands and ducts of the nipple. Hyperkeratosis and parakeratosis were absent. The similarity of the histologic changes to those described by Bowen in the cases of precancerous dermatitis recently reported by him are emphasized. The etiology of Paget's disease is still unknown, but the author suggests the hypothesis that the large amount of glycogen found by him in the Paget's cells might give rise to lactic acid which, acting as a chronic irritant, leads to the formation of carcinoma. He concludes that Paget's disease of the nipple is a precancerous, and not an actually carcinomatous condition, and that the Paget cells are proliferated epithelial cells which owe their characteristic appearance to the presence of glycogen. The carcinoma may arise from the epidermis, the epidermal appendages or the milk ducts.

O. T. SCHULTZ.

ENDOCRINE SYSTEM IN OSTEOGENESIS IMPERFECTA. T. FAHR, *Virchows Arch. f. path. Anat.* **261:732**, 1926.

In his examination of a stillborn, full term, female child with osteogenesis imperfecta, Fahr paid especial attention to the endocrine system, in which he described changes that he interpreted as an abnormal maturity of the organs of the system. The suprarenals were smaller than is normal in the new-born, and the medulla was relatively more prominent and gave a marked chrome reaction. The ovary contained well developed follicles. The medulla of the thymus was prominent, whereas in the normal child from birth to the fifth year the cortical zone is more prominent. In the thyroid, follicle and colloid formation were present, and the piling up of the epithelium in places was suggestive of hyperplasia. In the hypophysis there were numerous eosinophilous cells and much golden brown pigment which gave the iron reaction. Only the parathyroids were free of changes which the author could interpret as evidence of precocious maturity. Kaufmann's theory of the congenital dysfunction of the osteoblasts as the cause of osteogenesis imperfecta, Bauer's theory of congenital dysfunction of all supporting tissues, and the possible thyrogenous origin are discussed. Admitting that dysfunction of the osteoblasts is evidenced by its results in the skeletal malformations, Fahr believes that abnormality •

of the endocrine system in the form of a precocious maturity which is not compatible with life may be the more important fundamental factor. A theory based on a single case is not always easy to uphold. In an addendum to his article, Fahr describes briefly the observations in a second case of osteogenesis imperfecta in which the changes in the endocrine system were less marked, although evidences of abnormal maturity were unmistakable (unverkennbar) in the suprarenal, thymus and thyroid. Wider experience in the histologic examination of the endocrine organs of new-born infants showed that well developed graafian follicles are not unusual at birth, that eosinophilous cells may be numerous in the hypophysis at this stage and that the endocrine system may be variable in apparently normal new-born infants.

O. T. SCHULTZ.

EXPERIMENTAL CIRRHOSIS OF THE LIVER. G. LEITMANN, *Virchows Arch. f. path. Anat.* **261**:767, 1926.

In a series of rabbits whose ears had been treated with petroleum tar in toluol for the purpose of causing epithelioma, epithelial proliferation did not occur, but the liver was the seat of marked changes. The duration of the experiments was from one to four months. The surface of the organ was finely nodular and presented an appearance strikingly like that of human atrophic cirrhosis. The microscopic changes consisted of degeneration of liver cells with the presence of finely divided fat, material giving the iron reaction and vacuoles and of proliferation of interlobular stroma which had led in experiments of longer duration to the complete surrounding of individual liver lobules. In two of the animals, the liver was enlarged rather than decreased in size; in these exceptions there was regeneration of liver tissue. New formation of bile ducts occurred in the areas of most marked proliferation of interlobular stroma. Toluol alone did not cause similar changes.

O. T. SCHULTZ.

VITAL STAINING OF AORTA. M. GLASUNOW, *Virchows Arch. f. path. Anat.* **261**:837, 1926.

Okuneff, working in Anitschkow's laboratory, had found that the vital staining of animals with trypan blue led to characteristic patchy localization of the dye in the intima of the aorta, the localization being identical with that which Anitschkow, the proponent of the imbibition theory of lipoid infiltration in arteriosclerosis, had found in animals with experimental hypercholesterolemia (abstr., *ARCH. PATH.* **3**:114 [Jan.] 1927). Okuneff's results were obtained only in the cat and dog. In the rabbit, guinea-pig and cat the dye led to diffuse staining of the intima. Using the last named animals, Glasunow, also working under Anitschkow's direction, repeated the experiments, but modified the procedure in that the animals were not stained during life, but the aorta of the freshly killed animal was perfused with 1:20,000 trypan blue in oxygenated Locke-Ringer solution, a pressure of 75 cm. of water being used for rabbits 50 cm. for guinea-pigs and 40 cm. for rats. The perfusion periods varied from five minutes to one hour. After short periods of perfusion, from five to ten minutes for rats to twenty minutes for rabbits, there occurred a characteristic localization of the dye just beneath the openings of the various branches into the aorta, with minute points of color arranged in linear fashion between the mouths of the branches. With longer perfusion these points coalesced to form deeply stained streaks. The localization of the dye in linear streaks about the mouths of the branches of the aorta was therefore again identical with that

which Anitschkow had found for lipoids and confirms the latter's view of the greater permeability of the intima of the aorta to lipoids and other substances in those areas in which lipid deposition occurs earliest in spontaneous atherosclerosis.

O. T. SCHULTZ.

EPINEPHRINE HYDROCHLORIDE AND HEMOPOIESIS. M. MANDELSTAMM, Virchows Arch. f. path. Anat. **261**:858, 1926.

The injection of epinephrine hydrochloride is quickly followed by an increase in the number of leukocytes of the peripheral blood, the increase being diaphasic and involving first the lymphocytes and then the neutrophil leukocytes. The circulating monocytes are also moderately increased in number, but eosinophilous leukocytes do not show any change. Concerning the erythrocytes, previously published work leaves some doubt, but Platz described an increase of these also. Mandelstamm made a histologic study of the hemopoietic tissues of the rabbit following the injection of epinephrine hydrochloride. In one series of experiments, a single injection was made, and the tissues were examined at various intervals of from seven minutes to twenty-four hours. In another series the injections were repeated from two to thirty times. After single injections, active increase of the myelocytes, metamyelocytes and pseudo-eosinophils was apparent in the bone marrow within seven minutes, reached its height at one-half hour and was still evident at the end of twenty-four hours. Marked hypertrophy and hyperplasia of the reticulo-endothelium of the lymphoid tissues was already present at seven minutes and became associated somewhat later with increase in the number of large lymphocytes, many of which were in active mitosis. During these stages the capillaries and veins of the lymph nodes were filled with small lymphocytes. Hemocytoblasts were present in the myeloid and lymphoid tissues at twenty-four hours. The increase in circulating monocytes was believed to be due probably to multiplication of vascular endothelium. Repeated injections caused less marked changes. The dosages of epinephrine hydrochloride used were much greater than the amount which may be supposed to be present in the blood normally, and the author suggests that the changes noted by him may be part of a protective reaction against toxic amounts of epinephrine hydrochloride.

O. T. SCHULTZ.

ABOUT THE OBLITERATION OF THE GREAT ARTERIES. EDWARD MROZ, Polska Gaz. Lek., 1925.

This article contains the report of a case of obliteration of the common carotid and subclavian arteries in a syphilitic man, 49 years old. A left radial pulse was not present, but there was an advanced arteriosclerosis and chronic nephritis. Postmortem examination showed a marked syphilitic aortitis and an obliteration for 1 cm. from the beginning of the left common carotid and subclavian arteries by well canalized loose connective tissue.

ST. CIENCHANOWSKI.

TRACHEOPATHIA OSTEOPLASTICA. EDWARD SZCZELIK, Polska Gaz. Lek., 1926.

Tracheopathica osteoplastica, characterized by multiple bony, cartilaginous and osteochondral tumors of the tracheal mucosa, arises by a metaplasia of the mucosal connective tissue. An essential element in this metaplasia is a

cell found in hyaline connective tissue and characterized by a rod shaped nucleus. These cells actually form the bone, passing through a chondral stage in some instances, and in other instances omitting the intermediate chondral stage. All stages may be present simultaneously. Mechanical, thermal, and chemical stimuli are all suggested as influencing the mode of transition from connective tissue to bone. A natural predisposition of tracheal connective tissue to metaplasia is suggested as the basis for the changes.

ST. CIENCHANOWSKI.

PNEUMATOSIS CYSTOIDES INTESTINORUM. TADENSZ SKIBENEWSKI, Polska Gaz. Lek., 1926.

A man, 29 years old, with a clinical history of gastric ulcer, died of pneumonia following operation. Fifty cubic millimeters above the ileocecal valve and 1.5 to 2 cm. from the mesentery, there was a steel gray, flat swelling, 2 by 4.5 by 1.5 cm. It was composed of gas filled vesicles from microscopic size up to 1 cm. The gas was odorless. The vesicles were mostly in the subserosa but also in the submucosa, their walls being connective tissue, occasionally covered by a single layer of flat epithelial cells and rarely by giant cells. The frequent association of gas cysts with gastric and duodenal ulcers suggests the possibility of a similar etiology. Gas cysts are usually without clinical symptoms.

ST. CIENCHANOWSKI.

CYSTADENOMA PANCREATIS. TADENSZ SKIBENEWSKI, Polska Gaz. Lek., 1926.

A cystadenoma of the pancreas was observed in a man, aged 54, who had died of aortic aneurysm. In the body of the pancreas was a flattened multilocular cyst, 3 by 2 by 1.5 cm., each small cyst being filled with a transparent, pale yellow liquid, the largest cyst having a diameter of 6 mm. Except at one point, it was separate from the pancreatic tissue.

The cyst walls were composed of flat and cuboidal epithelial cells. The chemistry of the cystic fluid was not studied. Embryonic rests are mentioned as the possible origin of the neoplasm.

ST. CIENCHANOWSKI.

OBLITERATION OF THE PRINCIPAL HEPATIC VEINS. KAZIMIERZ SCIESINSKI and WITOLD KLEPACKI, Polska Gaz. Lek., 1926.

This article concerns an obliterative phlebitis of the hepatic veins in a 2 year old girl who was not syphilitic. The clinical diagnosis was tuberculosis and hepatic cirrhosis based on the clinical picture during a 10 months' illness. The postmortem diagnosis was: obliteration of the principal and median hepatic veins, passive hyperemia, fatty degeneration, focal necrosis and wide hemorrhages in the hepatic parenchyma. Pathologic changes and other conditions suggestive of syphilis were not present.

ST. CIENCHANOWSKI.

Pathologic Chemistry

CAROTINEMIA. WILLARD C. STONER, Am. J. M. Sc. 175:31, 1928.

The pigment was found in the blood stream in an adult. In adults carotinemia is unusual, while it is not uncommon in children on high vegetable diet. The cutaneous discoloration disappeared when foods rich in carotinoid were withdrawn from the diet.

CALCIUM STUDIES IN JAUNDICE. A. CANTAROW, S. M. DODEK and B. GORDON, Arch. Int. Med. 40:129, 1927.

The authors are of the opinion that in jaundice functional deficiency in calcium exists, probably due to the increased amount of bile pigments in the blood and tissues. The serum calcium values varied slightly, ranging from 9.3 to 12 mg. per hundred cubic centimeters in jaundice. There was an extremely wide variation, however, in the calcium content of whole blood, the figures ranging between 4.8 and 12 mg. per hundred cubic centimeters. Twelve hours after the administration of the parathyroid hormone the variation in the whole blood calcium of jaundiced and nonjaundiced patients was practically identical. Parathyroid extract acts as a mobilizer of calcium; in jaundice it tends to restore the normal distribution and functional availability of this element. The favorable effect of the hormone on the tendency of jaundiced tissue to bleed is due largely to the increased coagulability of the blood and probably to the diminished permeability of the capillary walls, the result of an increase in functioning calcium.

AUTHORS' SUMMARY (S. A. Levinson).

THE STORAGE OF WATER BY VARIOUS TISSUES OF THE BODY. H. SKELTON, Arch. Int. Med. 40:140, 1927.

The distribution of water in man and in the rat, dog, cat and rabbit shows that approximately half of the body water is in the muscles. The skin contains about one fifth of the water in the body, and the blood about 7 per cent. Of the water in the blood, 67 per cent is in the plasma and 33 per cent is in the corpuscles. All the tissues lost water after hemorrhage. The amount of water entering the blood came from the organs in the following order: A. In cats having a normal supply of water in their tissues: (1) muscle, 14.45 per cent; skin, 11 per cent; intestine, 3.6 per cent; liver, 3.5 per cent; spleen, 0.08 per cent. (2) Per hundred grams of tissue, the order was as follows: liver, 2.1 Gm.; intestine, 1.6 Gm.; skin, 1.2 Gm.; spleen, 0.8 Gm.; muscle, 0.5 Gm. B. In cats that had been deprived of water and food for five days: (1) skin, 43.5 per cent; muscle, 16 per cent; liver, 8.35 per cent; intestine, 2.6 per cent; spleen, 0.07 per cent. (2) Per hundred grams of tissue: skin, 3.6 Gm.; liver, 3.2 Gm.; spleen, 2.73 Gm.; intestine, 0.8 Gm.; muscle, 0.4 Gm. Following the injection of distilled water or hypotonic salt solutions, the fluid leaving the blood stream at the end of thirty minutes was distributed to the tissues in the following order: (1) muscle, 13-21 per cent; liver, 9.5-5.5 per cent; skin, 5.8-11 per cent; intestine, 2.7-4.5 per cent; spleen, 0.1-0.8 per cent. (2) Per hundred grams of tissue, the amount added was as follows: liver, 7.6-3 Gm.; intestine, 2.1-1.3 Gm.; spleen, 1.6-0.8 Gm.; skin, 1.1-1.9 Gm.; muscle, 0.7-1.1 Gm. Following the injection of isotonic and hypertonic sodium chloride solutions all tissues, except muscles, showed an increase in their water content. After isotonic sodium chloride, there was no change in the water content of muscle, while there was a decrease in its content after hypertonic sodium chloride was injected. The skin showed a greater increase in its water content the greater the sodium chloride content of the injected solution. Its increase per unit mass of tissue was least after distilled water and greatest after hypertonic sodium chloride was injected. Following the injection of 1.2 per cent calcium chloride solutions, the muscle and skin showed a decrease in their water content. Muscle showed the greatest difference per unit mass of tissue. The intestine showed an increase of 2.6 Gm. of tissue as compared to 2.4 Gm. for each hundred grams of tissue in the liver and of the spleen. The results after injecting 2.4 per cent calcium chloride were parallel to those after hemorrhage. Although the muscle contains nearly one half of the body water, and loses

the least per unit mass of tissue, it gives up more fluid than any other tissue when the animal is deprived of fluid, and takes up by far the greatest portion of any water added as water per se or as a hypotonic salt solution. The muscle is the most important water reserve of the body; it stores the greatest quantity of any excess, and acts as a safeguard against the loss of too much water from the body. The liver and the intestine appear to respond more quickly than any other tissues when there is an alteration in the water content of the body.

AUTHORS' SUMMARY (S. A. Levinson).

THE PROTEASES AND ANTIPROTEASES OF PLEURAL EXUDATES. CHARLES WEISS, *J. Infect. Dis.* **41**:467, 1927.

By the use of Northrop's formol titration technic the proteolysis of peptone and gelatin by various constituents of pleural exudates obtained from healthy rabbits after the intrapleural injection of starch and aleuronat was accurately measured. Both the leukocytes and the supernatant fluid digested peptone at different optimum p_H , and with gelatin peptic activity at p_H and tryptic action at p_H 8 was suggested. The hydrolysis of gelatin decreased when the enzyme solutions underwent active autolysis and the enzymes seemed to digest the proteins with which they were associated in the exudate rather than the gelatin. A mutual inhibition of digestive activity resulted from the reuniting of the supernatant fluid with the leukocytes. This inhibition ceased abruptly on the acid side p_H 5, and the suggestion is made that the compound formed between the inhibiting substance and the enzyme dissociates at the isoelectric point of serum albumin, with which the so-called antitryptic substance in rabbit plasma is associated.

AUTHOR'S SUMMARY.

ON THE EXPERIMENTAL TRANSMISSION OF ARSENIC TO THE AQUEOUS HUMOR. A. C. KRAUSE, A. M. YUDKIN and D. G. MORTON, *Proc. Soc. Exper. Biol. & Med.* **24**:385, 1926-1927.

Neoarsphenamine was injected into the jugular veins of dogs, following which the aqueous humor was drained off and tested for arsenic. The authors found that the normal aqueous humor does not contain arsenic. Only a trace of arsenic penetrates into the anterior chamber of the eye during the first few hours, and only the smallest measurable amount after twenty-four hours. Paracentesis definitely increases the permeability of the eye to arsenic. The bulk of the arsenic which accumulates after paracentesis apparently disappears within a few hours.

BENJAMIN RONES.

INSULIN AND HYPERCHOLESTERINEMIA. GEORGE FELLEGI, *Ann. de méd.* **22**:330, 1927.

Fellegi's observations on patients and also a careful survey of the literature lead him to the conclusion that insulin decreases the total amount of blood cholesterol in instances in which it is elevated. Insulin attenuates the functional insufficiency of the liver cell, increases the elimination of cholesterol and transforms a part of blood cholesterol into cholic acid. Insulin therefore interferes with the formation of calculi, and it spares the mucosa of the gallbladder from irritation, leading to a cure from hypercholesterinemia. Due to insulin, cholesterol and fat are fixed on the tissues. This hormone played an inhibitory rôle on the formation of cholesterol by the suprarenals. It finally calls forth the destructive function of organs on cholesterol.

B. M. FRIED.

A FOREIGN PROTEIN FROM THE PLACENTA IN THE NEPHROSIS OF PREGNANCY.
E. SCHWARZKOPF and H. SIEVERS, *Deutsche med. Wchnschr.* **53**:1303, 1927.

A Bence-Jones-like protein substance was extracted from the placenta of a somewhat macerated, stillborn fetus from a mother with nephrosis. The extract was nontoxic for the one white rat injected. Immunologic experiments were not described, nor were control examinations made of extracts from the normal placenta or from the placenta in other cases of toxicosis of pregnancy.

ARTHUR LOCKE.

STUDIES IN THE BEHAVIOR OF THE POTASSIUM AND CALCIUM CONTENT OF THE TOTAL BLOOD IN EXPERIMENTALLY ANEMIC ANIMALS. LEO KAUFHEIL and FRANZ KISCH, *Klin. Wchnschr.* **6**:1797, 1927.

The calcium content of the blood seems to be associated with a number of factors which as yet do not lend themselves to an exact interpretation. The potassium content of the whole blood is dependent on the erythrocyte content of the blood or on its hemoglobin content; it is therefore to be regarded as a "hematologic" factor and is related only with erythropoiesis and with disturbances of the erythrocytes.

E. F. HIRSCH.

CHEMICAL STUDIES OF THE ARTERIAL, CAPILLARY AND VENOUS BLOOD. KURT KARGER, *Klin. Wchnschr.* **6**:1904, 1927.

Blood from the A. radialis, ear lobe and V. mediana cubiti was analyzed quantitatively for total nonprotein nitrogen, uric acid, sodium chloride and sugar. The total nonprotein nitrogen coincided in 90 per cent of the three systems examined. The uric acid content agreed 100 per cent in all. The sodium chloride content varied somewhat. The values for arterial and capillary blood approximated, but only 65 per cent of agreement existed between arterial and venous blood. Sugar concentration on the average was 21 mg. per cent higher in the capillary than in the arterial and the venous blood.

E. F. HIRSCH.

QUANTITATIVE ESTIMATION OF BILE ACIDS IN THE SERUM WITH LIVER DISEASE.
K. SCHALSCHA and K. LANDÉ, *Klin. Wchnschr.* **6**:1939, 1927.

In various forms of liver disease with icterus the bile acid concentration of the serum ranges between 2 and 17 mg. per cent. With severe injury to the parenchyma of the liver the bile acid concentration of the serum diminishes or disappeared entirely. A proportionality between bile acid concentration and the size of the droplet in serum could not be demonstrated.

AUTHORS' SUMMARY.

CALCIUM CARBONATE BILE. R. DEMEL and W. SCHULZE, *München. med. Wchnschr.* **74**:363, 1927.

A woman, aged 33, was operated on for cholecystitis and cholelithiasis. The gallbladder was distended with thick, milky bile in which were found five small cholesterin-pigment-calcium stones. The milklike bile was nearly pure calcium carbonate. The acute inflammation of the mucous membrane of the bladder, coupled with an upset in the calcium metabolism, rendered calcium in the gallbladder nonabsorbable. This explains the presence of the calcium in the bile and in the concretions.

J. D. WILLEMS.

THE BLOOD SUGAR IN PULMONARY TUBERCULOSIS. H. AXHAUSEN, München. med. Wchnschr. 74:1752, 1927.

In 58 patients with a pulmonary tuberculosis, sugar concentrations of the blood ranged below and—in contrast to the results of the other authors—considerably above the normal variations, without any definite relations to the clinical and anatomic forms of the disease.

AUTHOR'S SUMMARY.

HYDROGEN SULPHIDE IN THE BLOOD WITH UREMIA. E. BECHER, München. med. Wchnschr. 74:1950, 1927.

With severe renal insufficiency and true uremia, hydrogen sulphide could not be demonstrated in the blood. The distillate of blood acidified, however, contains hydrogen sulphide. This is formed by the distillation. All tissue fluids by oxidation destroy in vitro added hydrogen sulphide. The disappearance of the added hydrogen sulphide is not dependent upon the formation of sulphhemoglobin. Whole blood destroys more than other tissue fluids. Repeated additions of hydrogen sulphide deplete the destroying property; boiling of the tissue fluids diminishes it. The destruction is rapid. The hydrogen sulphide destroying property of blood and other tissue fluids varies with different diseases.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

A MILK-BORNE EPIDEMIC OF POLIOMYELITIS. W. L. AYCOCK, Am. J. Hyg. 7:791, 1927.

The distribution of cases of poliomyelitis in the Broadstairs epidemic, in point of time, indicates that the majority of persons were simultaneously infected. The data concerning the four patients who left Broadstairs before the epidemic, with a high degree of probability, fixes a definite period of infection from which it may be inferred that the incubation period was in the majority of cases between six and fourteen days. The evidence concerning the milk supply points strongly to the milk furnished by one dealer as the common source of infection, and it further suggests that contamination of only one grade of his milk, which came from a single farm, was responsible for the epidemic.

AUTHOR'S SUMMARY.

THE SUSCEPTIBILITY OF FOWLS AND REPTILES TO THE VACCINE VIRUS. H. B. ANDERVONT, Am. J. Hyg. 7:804, 1927.

It is shown that newly hatched white Leghorn chicks are more susceptible to the vaccine virus than full grown chickens of the same variety. By utilizing this observation we are able to demonstrate: The correctness of earlier observations, i. e., that the fowl responds to infection with the vaccine virus by the production of Guarnieri bodies. That newly hatched chicks are susceptible to cutaneous, corneal and intracranial inoculation of the neurovaccine virus. That serial transmission of the neurovaccine virus through four chick brain passages can be accomplished. It is also shown that the vaccine virus can be carried through a series of three passages on the skin of two months old turtles. Typical Guarnieri bodies are observed within the skin and corneal lesions. These experiments show that the vaccine virus is capable of infecting animals of the order *Reptilia*.

AUTHOR'S SUMMARY.

VEGETATIVE ENDOCARDITIS DUE TO THE MENINGOCOCCUS. C. P. RHOADS, Am. J. Path. **3**:623, 1927.

A case of vegetative and ulcerative endocarditis due to the meningococcus is reported and the literature reviewed. The identity of the organism is proved, culturally and serologically. Lesions of the myocardium resembling those seen in rheumatic fever were obtained.

AUTHOR'S SUMMARY.

CHEMICAL STUDIES IN TUBERCULOSIS. LILIAN EICHELBERGER and K. LUCILLE McCLUSKEY, Arch. Int. Med. **40**:831, 1927.

The cell volume, especially in active cases of tuberculosis, is less than normal, and the size of the corpuscle is reduced. The cholesterol in the blood may vary; an increase appears to indicate resistance and a decrease lowering of resistance. Globulin is increased, and usually the total serum proteins are normal or higher.

HEMOLYTIC STREPTOCOCCUS CARRIERS: THEIR RELATION TO THE SPREAD OF SCARLET FEVER. MARY B. KIRKBRIDE and MARY W. WHEELER, J. A. M. A. **89**:1394, 1927.

Hemolytic streptococci producing potent toxins have been isolated from patients after recovery from typical scarlet fever, from thirty days to six months after the onset of the disease. Evidence has been obtained that occasionally typical cases of scarlet fever may occur as a result of contact with such convalescent carriers or with normal carriers.

AUTHORS' SUMMARY.

KALA-AZAR: DEMONSTRATION OF LEISHMANIA DONOVANI IN THE SKIN AND SUBCUTANEOUS TISSUE OF PATIENTS; POSSIBLE RELATION TO THE TRANSMISSION OF THE DISEASE. J. R. CASH and C. H. HU, J. A. M. A. **89**:1576, 1927.

In two cases of kala-azar Leishman-Donovan bodies were found in great numbers in the superficial tissues of the body—in one case the skin, and in the other the subcutaneous tissue. These changes are identical with those occurring constantly in experimental animals, in which the changes produced by kala-azar in the other organs parallel those seen in human cases. If lesions such as these are found to be present regularly in kala-azar, histologic study of the skin may be used as a diagnostic procedure instead of splenic puncture.

MALTA FEVER: WITH ESPECIAL REFERENCE TO THE PHOENIX, ARIZ., EPIDEMIC OF 1922. W. WARNER WATKINS and G. C. LAKE, J. A. M. A. **89**:1581, 1927.

The one instance of an epidemic of Malta fever in the United States was proved to be due to raw goat's milk. Malta fever is endemic in the goat raising district of the Southwest and should be constantly guarded against. A tabulation of forty cases of Malta fever shows the high specificity of the agglutination reaction and the constant leukopenia with mononucleosis. Malta fever may occur in every degree, from a mild ambulant type which may easily escape detection to very acute cases with abrupt onset, and it may persist in chronic form for from many months to several years. Only by bearing in mind the possibility of Malta fever and examining as a matter of routine the blood serums of all febrile patients can the presence of this disease be detected in a community. The sale of raw goat's milk should be prohibited. The demonstrated biologic relationship between the organisms of contagious abortion of cattle and hogs and the Malta fever in goats opens up important fields for epidemiologic and clinical observation.

AUTHORS' SUMMARY.

TULAREMIC PERITONITIS. S. C. FULMER and M. J. KILBURY, J. A. M. A. **89**:1661, 1927.

A man, aged 40, with a tularemic infection of the ring finger of the right hand, developed peritonitis with a greenish cloudy exudate from which *B. tularensis* was isolated.

THE STRUCTURE OF *BACILLUS ANTHRACIS* AND REVERSAL OF THE GRAM REACTION. JOHN W. CHURCHMAN, J. Exper. Med. **46**:1007, 1927.

The addition of small amounts of aqueous gentian violet, acriflavine, or acriviolet to suspensions of young cultures of *B. anthracis* reverses their gram reaction and diminishes their diameter about 40 per cent. The time required for these changes varies with the strain of *B. anthracis* examined. These changes are accompanied by a loss of weight. Ninhydrin positive substances are demonstrable in the filtrate from suspensions of *B. anthracis* to which dyes have been added. Similar changes are produced by these dyes in many, but not in all, of the sporogenic aerobes. Nonspore bearers are for the most part unaffected in these ways by the dyes, although to this statement there are a number of exceptions. The change in size produced by the dyes is demonstrable in hanging drop specimens as well as in stained smears, but not with equal constancy. Partial decolorizations of *B. anthracis* are described, which are produced by modifications of the Burke technic in which time of exposure to dye is shortened and time of exposure to decolorizer lengthened. The explanation for these phenomena which accords with all the known facts is that they depend on the existence in *B. anthracis* of a gram-positive cortex and a gram-negative medulla. Positive proof of the correctness of this explanation must await the evidence furnished by cross sections of bacteria.

AUTHOR'S SUMMARY.

FURTHER OBSERVATIONS ON THE SPECIFICITY OF THE GREEN-PRODUCING DIPLOCOCCUS IN MEASLES. RUTH TUNNICLIFF, J. Infect. Dis. **41**:267, 1927.

The green-producing diplococci isolated before the appearance of the rash in measles and during the acute stage of measles are immunologic distinct from nearly all similar cocci isolated during convalescence.

Measles cocci grown in normal and immune horse serum dextrose broth lose their specificity, as determined by the opsonic method. There specificity may be restored by transferring them on blood agar at 36 C. for a few generations.

Growing measles cocci at room temperature does not affect their specificity, but growth at 40 and 41 C. completely removes their specificity as determined by the opsonic method.

AUTHOR'S SUMMARY.

EFFECT OF DRYING ON THE SPECIFICITY OF SCARLET FEVER STREPTOCOCCI. RUTH TUNNICLIFF, J. Infect. Dis. **41**:272, 1927.

Scarlatinal streptococci, according to opsonic tests, lose their specificity through drying. This characteristic seems to be stable for about fifty generations, after transferring on moist blood agar. The drying of streptococci may explain why streptococci isolated from walls and floors of rooms occupied by scarlet fever patients do not seem to belong to the scarlatinal group of streptococci.

AUTHOR'S SUMMARY.

THE ETIOLOGY OF MEASLES. RUDOLPH GEGKWITZ, J. Infect. Dis. **41**:304, 1927.

The virus causing measles can be kept alive for several weeks outside the human system if blood of cases of measles is drawn just at the beginning of the rash and diluted in the proportion of 1:7 to 1:10 with buffered salt solution containing the same number of anions and kations and showing the same p_H as blood. This mixture must be kept at a temperature 0 C.

Measles produced by inoculation in the skin begins earlier than natural measles or measles following an artificial infection of the mucous membranes of the respiratory tract, furthermore, the symptoms are milder and of shorter duration. There seems to be an analogy between morbillisation against measles and variolation against smallpox.

Measles can be produced in human beings with material sterile from a bacteriologic point of view, with sterile blood of a patient with measles drawn at the right time, or with dilutions of such blood, which have passed through a Berkefeld filter. Sterile filtrates of nasal secretions collected in the pre-eruptive stage of the disease and diluted with physiologic sodium chloride solutions are also capable of producing measles.

Measles virus can be grown in vitro in culture mediums containing plasma from susceptible or immune persons which is diluted in a proportion of 1:6 or 1:7 with buffered physiologic sodium chloride solution. In order to keep the virus alive and to secure growth, it is necessary to associate it with living cells, such as slowly growing bacteria regularly found in cases of measles.

With sterile filtrates of cultures, reactions which are similar to measles can be provoked in human beings, the specificity of which can be proved by the fact that such persons are later immune against large amounts of infectious blood.

Monkeys (*Macacus rhesus*) can be made sick by injections of such material and the specificity of the reactions can be proved by the fact that their serum collected after the reaction can protect infected human beings against measles, while the serum of normal monkeys does not.

AUTHOR'S SUMMARY.

A GRAM-POSITIVE DIPLOCOCCUS IN HUMAN PROTOZOAL INFECTIONS. W. L. VOGEL, J. Infect. Dis. **41**:317, 1927.

A hemolytic gram-positive diplococcus differing immunologically from hemolytic streptococci and from the diplococcus of pneumonia, was found in the intestinal flora of 54 of the 119 cases of suspected amoebiasis. Protozoa were present in seventy-nine cases, with pathogenic species in fifty-nine, and in these the diplococcus was present in fifty-four (91.5 per cent). Intestinal lesions were produced in inoculated animals and the diplococcus recovered in turn from these lesions.

The optimum H-ion concentration for growth of the diplococcus approximates that reported by other authors for pathogenic protozoa, in vitro, and maximum denitrification takes place at this p_H range. Emetin hydrochloride and acetarsone (stovarsol) are not germicidal for the diplococcus, and the suggestion is made that this organism may be a contributory factor in the pathologic process and peculiar toxemia accompanying the protozoal infections, especially in those patients who fail to respond to treatment.

AUTHOR'S SUMMARY.

BACILLUS SORDELLII, A CAUSE OF MALIGNANT EDEMA IN MAN. IVAN C. HALL and JOSEPH P. SCOTT, J. Infect. Dis. **41**:329, 1927.

This paper confirms Sordelli's discovery of a new putrefactive pathogenic anaerobe in human gangrenous infections, which combines the virulent prop-

erties of *B. novyi* with the principal morphologic and cultural properties of *B. sporogenes*.

The binomial "*Bacillus sordelli*" is suggested as a more appropriate and less confusing name than "*Bacillus oedematis-sporogenes*" which Sordelli used.

Efforts to show that Sordelli's culture consisted of a mixture of different species were unsuccessful. It was possible, however, to isolate from one of his strains two substrains differing from each other in the form of colonies in deep agar, which are regarded as mutants or dissociates. Colonial differences, though at first apparently constant, were later shown to be temporary.

B. sordelli differs from *B. sporogenes* in pathogenicity, in motility, and in its slower and less complete proteolytic powers and from *B. novyi* in its more active proteolytic powers. It differs from both in the ability to form or accumulate tyrosine crystals in old protein cultures. It closely resembles *B. novyi* in the production of a soluble exotoxin and in the character of lesions produced in animals.

AUTHORS' SUMMARY.

TRANSMISSIBLE LYSIS OF A THERMOPHILIC ORGANISM. STEWART A. KOSER, J. Infect. Dis. 41:365, 1927.

A transmissible lytic agent for a thermophilic gram-positive spore-forming organism was found to possess the unusual feature of activity at high temperatures—optimum about 50 C. and persisting to 57 or 58 C.—which suggests a close relation between the principle and the organism itself.

AUTHOR'S SUMMARY.

THE INCIDENCE OF SCARLET FEVER STREPTOCOCCI IN THROATS OF DIPHTHERIA PATIENTS. PAUL S. RHOADS, J. Infect. Dis. 41:377, 1927.

Hemolytic streptococci were cultured from the throats or noses of 29 of a series of 100 patients who were admitted with the diagnosis of diphtheria to hospitals for contagious disease in Chicago.

Sixteen, or 55.2 per cent, of these strains of hemolytic streptococci, were identified as scarlet fever streptococci by the toxin neutralization method.

The strength of the scarlatinal toxin produced by these strains varied from 100 to 10,000 skin test doses per cubic centimeter. It was less than 2,000 skin test doses per cubic centimeter in 14 of the 16 strains.

Thirteen, or 44.8 per cent, of the strains of hemolytic streptococci isolated did not produce any demonstrable scarlet fever toxin. AUTHOR'S SUMMARY.

THE INCIDENCE OF CARRIERS OF *B. AERTRYCKE* (*B. PESTIS CAVIAE*) AND *B. ENTERITIDIS* IN WILD RATS OF SAN FRANCISCO. K. F. MEYER and K. MATSUMURA, J. Infect. Dis. 41:395, 1927.

As a part of a study of certain factors which may or may not be responsible for food infections and food poisoning outbreaks it appeared desirable to establish the existence and the incidence of rodent typhoid in the rat population of San Francisco. A bacteriologic examination of 775 rats (*Mus norvegicus*, *decumanus* and *rattus*) revealed 58 rodents which were infected either with *B. enteritidis* (28 cases) or *B. aertrycke* (30 cases). As far as published records permit of deductions, this study records for the first time the occurrence of *B. aertrycke* in wild rats. At least 17, or 2 per cent, of the rodents harbored the specific organisms in the intestinal tube and were capable of shedding highly virulent bacilli into the feces. Only two thirds of the infected rats exhibited lesions in the liver and spleen which might be considered the naked-

eye signs of a preceding infection. Since the animals came from districts in which no rat virus baits had been scattered it is clear that they derived the paratyphoid-enteritidis bacilli from natural infection. The carrier rate is fairly uniform throughout the city and is approximately 6 per cent in the vicinity of the slaughter houses, retail and second class residential districts. It is not unlikely that the conditions found in San Francisco are typical for a city with a vigilant rat extermination service and should not be considered as representative of the prevalence of rat typhoid in other large communities.

AUTHORS' SUMMARY.

THE FORMATION OF CONTRACTILE VACUOLES IN *AMOEBA PROTEUS*. H. C. DAY, J. Morphol. & Physiol. 44:363, 1927.

The history of investigations on the contractile vacuole is reviewed briefly and brought up to date.

The study of the contractile vacuole in *Amoeba proteus* is considered from standpoints of origin, structure, behavior, and function. The results are obtained from a prolonged study of normal organisms and from their reactions when introduced into conductivity water.

The origin of vacuoles is studied by means of dark-field illumination which reveals the vacuole to be formed from a fusion and coalescence of extremely minute droplets.

The retaining "wall" of the contractile vacuole is not a permanent structure, but is in the nature of a condensation membrane, totally disappearing with each contraction.

The loci of the contractile vacuoles is not permanent, but vacuoles are formed more or less at random. It is unlikely that they are supported in gelled areas, for amebae with a dozen vacuoles are active and there is no interference with ameboid movement.

Conductivity water increases the size, number, and rate of contraction of contractile vacuoles, which suggests that they may function in maintaining an osmotic gradient as well as in the elimination of metabolic waste.

AUTHOR'S SUMMARY.

PRELIMINARY NOTE ON THE EXPERIMENTAL STUDY OF ENZOOTIC ENCEPHALOMYELITIS (BORNA DISEASE). S. NICOLAU and I. A. GALLOWAY, Brit. J. Exper. Path. 8:336, 1927.

The virus of enzootic encephalomyelitis isolated by Zwick from horses and by Miessner from sheep was inoculated by various routes, mainly intracerebral, into rabbits, guinea-pigs, mice, rats, monkeys (*Macacus rhesus*) and ferrets. The rabbit proved most susceptible to infection. The two strains of virus appeared to be identical.

Rabbits displayed individual variation as regarded incubation period and duration of the disease. Young rabbits died sooner than old. Loss of weight, relative lymphocytic mononucleosis and absence of fever were noted. The symptomatology was characteristic of encephalomyelitis sometimes resulting in general paralysis. Death occurred in from twenty-eight to thirty-six days following inoculation. The disease was produced not only by intracerebral inoculation, but also by the intrasciatic and intratesticular routes.

The histologic changes in the central nervous system were those of typical encephalomyelitis plus profound changes in the spinal ganglia and peripheral nerves. The lesions were of two orders — infiltrative and degenerative. The

reacting cells of the meningitis of the parenchymatous and perivascular infiltration were always mononuclear. Satellism and degeneration of the nerve cells and neuronophagia were marked in the medulla, midbrain and spinal ganglia. The nerve roots and descending peripheral nerves showed interstitial and perivascular infiltration. The corpuscles of Joest-Degen were found not only in the cornu ammonis, but also in the cerebrum, medulla, anterior horns of the spinal and the spinal ganglia. Oxyphilic corpuscles were present in nearly every portion of the nervous system.

An immunity, lasting as long as 160 days, was conferred on rabbits by the intracerebral inoculation of a suitably attenuated virus. Attenuated horse virus immunized rabbits against sheep virus.

A monkey died seventy-three days after intracerebral inoculation with virus of rabbit passage, developing the symptoms and exhibiting the lesions characteristic of encephalomyelitis, ganglioradiculitis, and peripheral neuritis.

S. D. SIMON.

THE LOCAL FATE OF TETANUS SPORES INOCULATED INTO GUINEA-PIGS. DOROTHY S. RUSSELL, Brit. J. Exper. Path. 8:377, 1927.

By subcutaneous inoculation of guinea-pigs, it was found that either toxic or nontoxic spores of tetanus bacilli will produce an initial infiltration of polymorphonuclear leukocytes which engulf a large percentage of the spores. Subsequently, these reacting cells disappear and the large mononuclear phagocyte predominates in the lesion. But phagocytosis is never complete, there always being a few extracellular spores. As time elapses, the large phagocytes combine to form foreign body giant cells and many spores may be seen in their cytoplasm. Finally, the lesion heals; the animal does not die.

If, however, the spores, toxic or nontoxic, be mixed with a heavy suspension of sterile earth, the initial reaction is much more intense and an abscess forms, in the necrotic center of which the spores form bacilli. Phagocytosis is even less complete and there is considerable necrosis. If the spores be nontoxic the vegetation reaches its maximum, giant cells are formed and then the lesion declines. If toxic spores are used the animal dies at the height of the vegetation on the fourth day.

The substitution of calcium chloride for sterile earth causes widespread necrosis with rapid vegetation throughout this area.

A method is given for staining tetanus spores in the tissues.

PEARL ZEEK.

THE CONDITIONS UNDER WHICH TETANUS SPORES GERMINATE IN VIVO. PAUL FILDES, Brit. J. Exper. Path. 8:387, 1927.

The author finds that by ligating one of the testicles of a guinea-pig and then injecting a suspension of tetanus spores into it he can obtain an unusually active vegetation in as brief a time as two hours, which is before any histologically detectable necrosis has occurred. He attributes this phenomenon to the low oxygen tension in the ligated tissue. A similar injection into the unligated testicle does not show vegetation at any time. The author further believes that phagocytosis is an unrelated, indifferent phenomenon as regards vegetation, since spores are seen for considerable periods in the tissues without phagocytosis and without germination.

PEARL ZEEK.

ICTEROHEMORRHAGIC SPIROCHAETOSIS OF THE CHIMPANZEE TRANSMISSIBLE TO MAN. R. WILBERT and M. DELORNE, Ann. de l'Inst. Pasteur **41**:1139, 1927.

The authors report from French Guiana a spirochete, provisionally called *Spirochaeta anthropopithecii*, n. sp., pathogenic for the chimpanzee and for man. Emulsions from the spinal cord seem more virulent than liver emulsions or blood. Vaccines, heated at 55 C., seem to produce immunity. It is of interest in general and comparative pathology and in tropical epidemiology, and offers interesting analogies with certain other spirochetal diseases. The organism moves slowly, rotating; it assumes a C or an S shape; it has 2.5 spirals, and measures from 6 to 7 by 0.2 to 0.3 micron.

M. S. MARSHALL.

THE BACTERIOLOGY OF PERITONITIS FOLLOWING PERFORATION OF GASTRIC, DUODENAL AND JEJUNAL ULCERS. D. VON WENDT, Arbeit. a. d. Path. Instit. d. Univ. Helsingfors. **4**:131, 1926 (new series).

Material obtained at operation from fourteen male patients from 23 to 62 years of age was studied by direct smears and aerobic, aerobic-anaerobic, and strictly anaerobic methods. Eleven patients with a perforated gastric ulcer, were operated on from two to nine hours after perforation, with one exception in which forty-eight hours elapsed, and all but two recovered. Of three patients with a perforated duodenal ulcer, one died, and one patient who had a perforated jejunal ulcer following a gastro-enterostomy for gastric ulcer, recovered. Twenty-three per cent of the cultures remained sterile. In the nonsterile cultures, 90 per cent were nonhemolytic streptococci. The conclusions are: The bacterial flora of "ulcer" peritonitis is a reduced and somewhat modified mouth flora. The number of bacteria is of little significance, and they are usually a low virulence type. The dominant bacteria are non-hemolytic streptococci. The formulation of a prognosis is not made easier by a bacteriologic examination of the peritoneal cavity.

G. RUKSTINAT.

ON THE PRESENCE OF YEASTLIKE FUNGI IN NORMAL THROATS. FRED W. TANNER, ESTER N. LAMPERT and MAX LAMPERT, Centralbl. f. Bakteriologie. **103**:94, 1927.

The authors, in a study of yeastlike organisms recovered from 1,002 apparently normal throats, report finding the organisms in 10 per cent of the throats examined. These organisms were not the types used in fermentation industries and many showed pathogenic properties for white mice.

PAUL R. CANNON.

FILTRABLE FORMS OF THE TIMOTHY BACILLUS. W. JELIN, Centralbl. f. Bakteriologie. **103**:325, 1927.

Jelin reports that he has been able to pass five and six day cultures of timothy bacilli mixed with staphylococci, through Chamberland filters and recultivate acid-fast forms of the former.

PAUL R. CANNON.

THE CULTIVATION OF THE TUBERCLE BACILLUS AND ITS USE IN THE DIAGNOSIS OF TUBERCULOSIS. JOSEPH HOHN, Centralbl. f. Bakteriologie. **103**:342, 1927.

The author defends the value of his sulphuric acid method in the preparation of tuberculous material for cultivation. He discusses the technical requirements of his method and concludes that it is one of the safest and simplest bacteriologic methods available for this purpose.

PAUL R. CANNON.

THE CULTIVATION OF TUBERCLE BACILLI IN PRACTICAL DIAGNOSIS. KURT MEYER, *Centralbl. f. Bakteriol.* **103**:345, 1927.

Meyer states his experiences with the antiformin and sulphuric acid methods of purification of tuberculous material. One point he stresses particularly is that many times acid-fast bacilli may be found on the culture medium from four to seven days after inoculation and this forms the main advantage of the cultural methods over animal inoculations.

PAUL R. CANNON.

FURTHER INVESTIGATIONS AS TO THE RÔLE OF BUGS IN THE EPIDEMIOLOGY OF RELAPSING FEVER. H. P. ROSENHOLZ and M. J. GILBERT, *Centralbl. f. Bakteriol.* **103**:348, 1927.

The authors report further experimental studies as to the possible rôle which *Cimex lectularius* plays in the transmission of relapsing fever. Bugs were starved and then fed on a mouse infected with relapsing fever. The bugs were then put in a flask at 23 C. and fed every four days on healthy mice. At certain intervals, the eggs and larvae were collected and examined and in no case were spirochetes found. They also found that the spirochetes remain alive at temperatures at which the bugs die, and that the spirochetes may survive in the fasting bug for several months.

Bugs were injected into the hemolymph with various spirochetes and trypanosomes and it was found that the injected organisms persisted there for many days, thus suggesting the possibility that other infections may be transmitted by bugs.

PAUL R. CANNON.

CYTODIAGNOSIS IN AFFECTIONS OF THE LARGE INTESTINE. A. ALEXEIEFF, *Centralbl. f. Bakteriol.* **103**:354, 1927.

This paper, with two plates, deals mainly with a discussion of the value of a microscopic examination of the pus in the stools of patients with bacillary and amebic dysentery and with ulcerative colitis. Alexeieff maintains that by a differential count, his so-called pyogram, it will be found that in bacillary dysentery one will find from 97 to 98 per cent neutrophils; from 1 to 2 per cent eosinophils and an occasional plasmophage, whereas in amebic dysentery, there will be from 20 to 30 per cent neutrophils; from 1 to 2 per cent eosinophils; a few plasmophages, and from 70 to 80 per cent small lymphocytes. In ulcerative colitis, the picture is almost identical with that of bacillary dysentery. He then discusses the possible etiology of ulcerative colitis and the mode of action of emetine in amebic dysentery, concluding that emetine is actually a parasiticide. In regard to the question of local eosinophilia he concludes from the finding of eosinophilic myelocytes in the wall of the intestine, although at the same time there is no eosinophilia in the blood, that they actually arise locally from the intestinal wall.

PAUL R. CANNON.

EXPERIMENTAL MENINGITIS FROM A CASE OF INFLUENZAL MENINGITIS. HANS DEMME, *Centralbl. f. Bakteriol.* **103**:363, 1927.

Demme reports a case of meningitis in which organisms of *B. influenzae* type were found in the spinal fluid. These organisms were not markedly hemoglobinophilic and ceased to grow on blood agar after the fourth transfer. They showed pronounced pleomorphism. Injection of the spinal fluid subdurally in rabbits led to an increased cell count in the spinal fluid with leptomeningitis and slight encephalitis. He discusses the possibility of a spontaneous encephalitis having been induced by the injected material.

PAUL R. CANNON.

CONGENITAL MALARIA. LJACHOWETZKY, *Centralbl. f. Bakteriologie*. **103**:380, 1927.

The author analyzes his material obtained from thick blood smears of mothers and their new-born children, and he concludes that a direct transfer of malaria from the mother to the child occurs through the placenta. He points out that in view of this fact, it is necessary in the campaign against malaria to treat pregnant malarial carriers in order to prevent the birth of children who may constitute a new series of malarial carriers.

PAUL R. CANNON.

BOVINE ANAPLASMOSIS IN RUSSIA. W. L. YAKIMOFF and W. L. BÉLAWINE, *Centralbl. f. Bakteriologie*. **103**:419, 1927.

The authors describe an infection with an anaplasma in a cow at Piatigorsk. The symptoms were fever, icterus and marked anemia. In the erythrocytes, anaplasmas were found, mostly marginal in type. A table gives a comparison of this form with others previously described, as to size, numbers in erythrocytes, percentage of erythrocytes affected, red cell count, symptoms and other factors. The authors suggest calling the organism *Anaplasma rossicum*, n. sp.

PAUL R. CANNON.

INVESTIGATIONS ON HERPES SIMPLEX AND ZOSTER. HELMUTH FREUND and BRUNO HEYMANN, *Ztschr. f. Hyg. u. Infektionskr.* **107**:592, 1927.

In eight cases of herpes genitalis the authors obtained seven highly virulent and neurotropic strains by simultaneous inoculation into the cornea of rabbits and the plantar surface of guinea-pigs. In all seven cases the infectious material was derived from recently developed clear vesicles, while the eighth strain coming from an ulcerated vesicle was only slightly virulent. In eight cases of extragenital herpes (three from the cheek, two from the lips, one from the nose, one from the finger and one from the buttocks) they obtained three highly virulent, neurotropic strains (from finger, nose and buttocks), while the others were of a lower degree of virulence. The infectious material of the three virulent strains was again derived from recent clear vesicles. The virulence, therefore, does not depend on the location of the lesion, but on the condition of the vesicles which are used for inoculation. In any event, no constant difference was found in virulence between genital and extragenital herpes. In guinea-pigs, the neurotropic strains may produce large torpid ulcers on the plantar surface of the foot; it is thought that they are due to trophic nervous disturbances. Inoculation with material from herpes zoster was less successful. In a third of the cases, after preputial inoculation in guinea-pigs, the development of delicate vesicles was observed which disappeared soon and sometimes recurred. The presence of herpes virus could not be demonstrated in these experimental vesicles. No result was obtained from corneal, plantar and preputial inoculation of material from chickenpox.

W. OPHÜLS.

FORMATION OF RADIAL ROWS OF CLUBS ABOUT DEAD TUBERCLE BACILLI AS A REACTION OF THE HOST. K. MEYER and E. MAYER, *Ztschr. f. Hyg. u. Infektionskr.* **108**:38, 1927.

The authors succeeded in producing actinomyces-like aggregations surrounded by radially arranged clubs in rabbits by intravenous injection of clusters of dead tubercle bacilli. Since the bacilli had been killed by live steam, and the fact that they were dead had been established by guinea-pig inocula-

tion, it seems evident that the clubs cannot have been formed by the bacilli. Their observations seem to show that the clusters of bacteria are first enveloped by a layer of gelatinous material which later breaks up into clubs. They refer to a recent paper by Levaditi and Dimanesco who obtained typical club formation in rabbits as a result of the intramuscular injection of tellurium suspended in oil, and who come to the conclusion that the development of clubs is a nonspecific reaction on the part of the host to the presence of various bacteria, and even of inorganic substances.

W. OPHÜLS.

FURTHER EXPERIMENTS ON THE DISSEMINATION OF MICROORGANISMS IN THE FORM OF DUST, PARTICULARLY OF INFLUENZA BACILLI. B. LANGE and E. JOCHIMSEN, *Ztschr. f. Hyg. u. Infektionskr.* **108**:66, 1927.

Lange has continued his experiments on the dissemination on bacteria in dust and comes to the following conclusions: Dust containing bacteria may form immediately after soiling an object with infectious sputum. While large amounts of dust are only developed by strong mechanical influences, a certain quantity of it is produced by the ordinary handling of materials in living rooms. Living bacteria are present not only in the coarse visible dust, but also in the fine invisible dust coming from clothes or handkerchiefs. The invisible dust remains suspended in the air for some time. In experiments with floor dust, he found 14 per cent of the bacteria still floating in the air after five minutes, and 1 per cent after thirty minutes. In experiments with handkerchiefs, the corresponding figures were much higher—46 per cent after five minutes and 12 per cent after thirty minutes. The floating infectious dust consists to a large extent of free bacteria. Even bacteria which are easily destroyed by drying such as the influenza bacilli can be carried in dry dust and can cause infection in this manner.

W. OPHÜLS.

EXPERIMENTAL INVESTIGATIONS ON THE INFLUENCE OF SCURVY ON THE DISPOSITION TO INFECTIONS. P. SCHMIDT-WEYLAND and W. KÖLTZSCH, *Ztschr. f. Hyg. u. Infektionskr.* **108**:199, 1927.

Schmidt-Weyland and Költzsch found that guinea-pigs suffering from experimental scurvy proved to be much more susceptible to bacterial infection than normal ones. It was immaterial whether the infectious agents were introduced by inhalation or ingestion. In scorbutic animals which had not been infected experimentally, they almost always found spontaneous infections. These were most frequently caused by the types of bacteria which are concerned in the production of natural epidemics among guinea-pigs in captivity, namely to the bacteria of chicken cholera or to pneumococci. The nature of the organisms producing the spontaneous infections seemed to vary with the seasons. Attention is called to the bearing of these experimental observations on epidemics among human beings.

W. OPHÜLS.

TETANOPASMIN AND TETANOLYSIN. G. C. REYMAN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **50**:405, 1927.

This paper of fifty-four pages describes a detailed study of the conditions governing the formation of tetanospasmin and tetanolysin. PAUL R. CANNON.

STUDY OF THE MUTATION OF STREPTOCOCCI. A. KUROKAWA, *Tohoku J. Exper. Med.* **9**:355, 1927.

Cultures of streptococci were sterilized by exposure for one-half hour to a dilution of 1:5,000 dilution of rivanol. The antiseptic action of the solution

was dissipated by contact with erythrocytes, kaolin or charcoal, probably by absorption which according to animal experiments, is of a looser combination with the charcoal. Certain strains of hemolytic streptococci influenced by dilute solutions of rivanol develop green-producing colonies, while others are persistently hemolytic. By repeated animal passage the green-producing streptococci were changed back to hemolytic with parallel virulence. The splitting off of green-producing-avirulent strains and of hemolytic-virulent strains from hemolytic streptococci by passage through animals as reported by Schnitzer and Munter, is considered to be only a part of the complete phenomenon of the return of all green streptococci to hemolytic virulent organisms if passage is continued long enough.

Rivanol is an acridine derivative, described by Morgenroth, Schnitzer and Rosenberg (*Deutsche med. Wchnschr.* **47**:1317, 1921) similar to acriflavine and proflavine.

ETHEL B. PERRY.

Immunology

LABORATORY DIAGNOSIS OF SMALLPOX VIRUS. NEIL E. MCKINNON and ROBERT E. DEFRIES, *Am. J. Hyg.* **8**:93 and 107, 1928.

The intradermal injection of material from smallpox causes a definite lesion in normal rabbits, but material from chickenpox does not have such an effect. In a vaccine immunized rabbit, the course of the reaction to smallpox material differs from that in the normal rabbit.

A RAPID METHOD FOR THE MACROSCOPIC AGGLUTINATION TEST. ARLYLE NOBLE, *J. Bact.* **14**:287, 1927.

In the test described, 0.1 cc. of bacterial suspension containing five times the number of organisms in the suspension used in the standard eighteen hour agglutination test, was added to 0.1 cc. of serum dilution; the mixture was slowly shaken for two minutes, then made up to 1 cc. with salt solution and read at once. Minor variations of this technic were made according to the organism (pneumococci, meningococci, typhoid, paratyphoid A and B, dysentery and anthrax bacilli): the antipneumococcic serum, for instance, whether for typing or for titration tests, was added without dilution in amounts from 0.1 to 0.01 cc. directly to the heavy suspension, and all salt solution was added after shaking. The readings thus obtained agreed with those of the standard test in which the same actual amounts of cells and serum are used, but in dilute solutions of consequently greater volume. The advantages of a rapid method both for diagnostic and experimental use was pointed out.

FURTHER STUDIES ON BACTERIAL ALLERGY: THE ANTIGEN INVOLVED IN PNEUMOCOCCUS ALLERGY. HANS ZINSSER and FRANCIS B. GRINNELL, *J. Bact.* **14**:301, 1927.

Autolysates of washed pneumococci suspended in a small quantity of salt solution (with thymol, phenol or toluene) and incubated, and likewise bile solutions of pneumococci were found more effective in sensitizing and eliciting skin reactions in guinea-pigs than were either whole pneumococci or their extracts. Sensitization of the skin of guinea-pigs not initially reactive was accomplished in from five to seven days by daily injections of from 0.1 to 0.2 cc. of the autolysate. Corresponding sensitiveness of other tissues was not revealed by intraperitoneal injections. The responsible substance was present in the clear supernatant fluid of the autolysate and was heat stable. Serums from animals sensitized or immunized with autolysates had little

neutralizing action and no relation seemed to exist between this and the agglutinating action. Group specificity rather than type specificity is claimed. Suggestions are made that similar autolysis and consequent sensitization may occur during pneumococcic infection.

FURTHER STUDIES ON THE TRANSPLANTATION OF THE LARVAE OF *TAENIA CRASSICOLLIS* AND THE EXPERIMENTAL PRODUCTION OF SUBCUTANEOUS CYSTICERCUS SARCOMATA. F. D. BULLOCK and M. R. CURTIS, J. Cancer Research **10**:393, 1926.

Taenia larvae at an early stage of development stimulate to active cell proliferation the mesothelial cells of the liver or groin of rats or mice. This activity gradually subsides, but the cells differentiate into a fibrous cyst wall around the parasite. In the rat, at least, such cyst walls either in the liver or groin may undergo sarcomatous transformation.

Slightly older *Taenia larvae* surrounded by rudimentary or early fibrous cyst walls may be transplanted from the liver of the rat to the groins of rats or mice. The larvae continue to develop at about their normal rate and remain constantly surrounded by cyst walls but do not reproduce the characteristic cell proliferation in the new host. The walls of these groin cysts resemble the walls of the cyst of about the same age in the liver or those formed in the groin around larvae transplanted before encystment. Whether or not the cells of the original host persist and undergo proliferation has not been determined, although this seems possible. No animals with these cysts have yet reached the age of high cancer frequency in rats, but it is interesting to speculate on the possibility of the cells of one individual under the stimulation of a specific parasite being able to grow, differentiate, and undergo malignant transformation after transplantation to another individual of the same or another species.

AUTHORS' SUMMARY.

ACTION OF *B. WELCHII* TOXIN AND OTHER HEMOTOXINS OF ERYTHROCYTES IN VIVO. GUILFORD B. REED, J. H. ORR and C. MARION SPENCER, J. Infect. Dis. **41**:283, 1927.

It may be concluded from the data presented that the injection of *B. welchii* toxin into rabbits results in marked destruction of red blood cells, accompanied by definite variations in size. The injection of tetanolysin, staphylolysin, streptolysin and the hemotoxin of pneumococci in doses sufficient to produce an equally marked decrease in circulating red cells does not result in any measurable alteration in the size or the form of the remaining cells.

AUTHORS' SUMMARY.

ACTION OF *B. WELCHII* TOXIN AND OTHER HEMOTOXINS ON ERYTHROCYTES IN VITRO. GUILFORD B. REED and J. H. ORR, J. Infect. Dis. **41**:289, 1927.

B. welchii toxin mixed with fresh defibrinated rabbit blood produces rapid destruction of erythrocytes, accompanied by a definite variation of size. But in contrast with the action in vivo in which both microcytes and macrocytes are produced, the direct reaction in vitro results only in microcyte formation.

Tetanolysin and streptolysin in concentrations which produce similar amounts of hemolysis, when mixed with fresh defibrinated rabbit blood do not produce measurable variation in the size of the unhemolyzed cells.

This action of *B. welchii* toxin on red cells in the test tube seems comparable with the initial stages of the action of the toxin in vivo. In every

case of welchii toxemia in rabbits, whether following the injection of toxin or accompanying an infection which has been observed sufficiently early, there has been a primary development of microcytes which have persisted throughout the period of decreasing red cell numbers, but it has generally been observed that the minimum size of the red cells is reached and followed by some increase in size while the count is still falling. This is similar to the *vitro* observations which have just been described.

In the living animal, however, if it survives the primary anemia, during the period of stationary minimum numbers of red cells, or particularly during the period of increasing concentration of red cells in the blood, the microcytes are gradually replaced to a large extent by macrocytes, many of which exhibit polychromatic staining, poikilocytes and nucleated red cells. This latter condition is evidently associated with erythrocyte regeneration and has not been observed in the test tube experiments.

AUTHORS' SUMMARY.

A COMPARISON OF REACTIONS TO DERMOVACCINE AND TO NEUROVACCINE FOR SMALL-POX. STANLEY THOMAS, *J. Infect. Dis.* **41**:336, 1927.

In the 100 cases studied, all reactions—immune, vaccinoid and vaccinal—obtained with neurovaccine, were milder than the corresponding reactions with the ordinary dermovaccine. In no case did a hemorrhagic pustule result, and in every instance of pustulated accelerated reaction or vaccinia a clean, hard, nonitching scab formed quickly with almost no surrounding erythema. On revaccination with a high potency dermovirus, men vaccinated five months before with neurovirus did not show so high a degree of protection against the dermovirus as men who had previously (five months) been vaccinated with dermovirus. These men did, however, show considerably more immunity than men who had not been vaccinated within three years. Definite conclusions regarding the efficacy of neurovaccine do not yet seem justified.

AUTHOR'S SUMMARY.

THE OPTOCHIN-FASTNESS OF PNEUMOCOCCI. CLAUS W. JUNGELBLUT, *J. Infect. Dis.* **41**:345, 1927.

Studies of cellular changes of a pneumococcus type 1 strain adapted to optochin, did not disclose any characteristic properties which could be attributed to the adaptive process.

A nonadapted pneumococcus type 1 strain in the presence of sterile filtrates of an optochin-fast variety of the same strain may occasionally exhibit a specifically increased tolerance for optochin in the next passage.

Optochin-fastness manifested by a nonadapted pneumococcus strain in the presence of filtrate from a fast pneumococcus strain does not seem to be associated with biologic changes in the nonadapted pneumococcus cell.

AUTHOR'S SUMMARY.

PREPARATION OF SALMONELLA PULLORUM ANTIGENS FOR COMPLEMENT-FIXATION TESTS. L. D. BUSHNELL and C. B. HUDSON, *J. Infect. Dis.* **41**:383, 1927.

The described method of preparing antigens has given a satisfactory product to be used for the complement-fixation test. The cell suspension washed carefully with ether is satisfactory in its antigenic action and is not anti-complementary, but causes a turbidity which makes tests difficult to read. The salt solution washings of the bacterial cells are antigenic and not anti-complementary after the second treatment. A very vigorous washing is necessary to cause dissociation of this product.

An unfiltered medium containing sodium citrate gives a more luxuriant growth than a medium which has been filtered. The citrate salt holds the phosphates in solution during sterilization.

AUTHORS' SUMMARY.

COMPLEMENT-FIXATION AND AGGLUTINATION TESTS FOR *SALMONELLA PULLORUM* INFECTION. L. D. BUSHNELL and C. B. HUDSON, J. Infect. Dis. **41**:388, 1927.

A highly antigenic substance may be separated from the cells of *Salmonella pullorum* by washing with salt solution. This substance is soluble in salt solution, is thermostable, and does not act freely in complement-fixation tests unless it is separated from the cells. All cultures of the organisms are not equally rich in this substance.

The complement-fixation and agglutination tests have about the same value in testing for carriers of *S. pullorum*. A combination of the two tests is more decisive, leaving a smaller number of questionable cases. The complement-fixation test cannot be used with low dilutions of serum and is of no special value in detecting actual carriers of the organisms.

AUTHORS' SUMMARY.

THE IMMUNOLOGIC RELATIONS OF TYPE 4 PNEUMOCOCCI OBTAINED DURING AN EPIDEMIC. G. H. ROBINSON, J. Infect. Dis. **41**:417, 1927.

Strains of type 4 pneumococci obtained during an epidemic could be resolved into a number of immunologic groups varying in their relative virulence toward man. During this period of the excessive incidence of type 4 the infection was caused by a few type 4 subgroups. The evidence indicated that epidemic strains could be classified while those from the sputum of normal individuals are probably more nearly heterogeneous. The epidemic groups obtained may be rare fixed types peculiar to certain localities. Normal sputum strains are sometimes obtained by the mouse test while the strains causing the infection in the patient is entirely missed.

AUTHOR'S SUMMARY.

THE DURATION OF IMMUNITY TO *B. WELCHII* TOXIN IN RABBITS. GUILFORD B. REED and MARION SPENCE. J. Infect. Dis. **41**:428, 1927.

It has been shown that the injection of *B. welchii* toxin into rabbits in doses sufficient to produce a definite anemia is followed, after one to two doses, by the establishment of an immunity. The immunity remains unimpaired for more than seven weeks, but shows a conspicuous decrease after from four to seven months.

AUTHORS' SUMMARY.

NONSPECIFIC WASSERMANN AND AGGLUTININ REACTIONS WITH SERUMS FROM PATIENTS WITH FEBRILE DISEASES. MARION CORRIGAN, J. Infect. Dis. **41**:457, 1927.

With serums from 100 patients with febrile diseases, two strongly positive Wassermann reactions were unaccountably obtained in cases of pneumonia with no syphilitic histories, and in one of these the Wassermann reaction became negative after the crisis; one strongly positive reaction was observed in a nonsyphilitic case of endocarditis; and a weakly positive reaction (two plus with cholesterol antigen) occurred in a case of epilepsy. A 1:40 agglutination and a two plus fixation with *B. typhosus* occurred in two cases of pneumonia without history of typhoid immunity. The serum of two patients with typhus agglutinated *B. typhosus*. The serum of a patient who proved not to have typhus agglutinated *B. proteus* X in a dilution of 1:640.

Reactions of an apparently false nature were thus observed to occur with serums of patients with high temperatures, but on so few occasions that a causal relationship of the temperature may be doubted. The temperature, on the other hand, may be instigative of a latent syphilitic condition or of the fluctuation of nonspecific agglutinating antibodies. In the latter case antityphoid vaccination or recovery from a mild attack of typhoid cannot be excluded with absolute certainty.

Nonspecific reactions occur so infrequently that their possible occurrence should not bar the routine use of the Wassermann or other serologic reaction for diagnostic purposes.

AUTHOR'S SUMMARY.

IS THE ANTIGENIC ACTION OF HEMOGLOBIN DUE TO HEMOGLOBIN? LUDVIG HEKTOEN and KAMIL SCHULHOF, *J. Infect. Dis.* **41**:476, 1927.

The antigenic group of hemoglobin forms a part of the molecule which may be split off by acids. It is probable that this antigen is globin, although the possibility of the presence of a third group is not yet excluded.

AUTHORS' SUMMARY.

DIPHTHERIA TOXOID-ANTITOXIN FLOCCULES. A. T. GLENNY and C. G. POPE, *J. Path. & Bact.* **30**:587, 1927.

Toxoid-antitoxin floccules are as good antigens as toxin-antitoxin floccules. The use of toxoid frees the preparation from all possible danger of increase in toxicity. The antigenic efficiency of the floccules is increased by heating to 80 C. for one hour.

AUTHORS' SUMMARY.

STUDIES ON STREPTOCOCCUS HEMOLYSIN. E. CÉSARI, L. COTONI and J. LAVALLE, *Ann. de l'Inst. Pasteur* **41**:919, 1927.

Hemolyzing substances are produced by various strains of streptococci both in cultures and in vivo. An excess of glucose prevents hemolysis. The hemolyzing substance appears in aerobic and anaerobic cultures; it develops at an optimum temperature of 37 C., is destroyed by heat and by antiseptics, and passes through filters. Its nature is unknown. It disappears gradually at intervals varying with the strain used, in some from the seventh to the sixteenth hour. Intravenous injections produce hemolysis in vivo, in rabbits provoking the appearance of antistreptolysins. "This negative character appears . . . of great importance and suffices to separate to the actual hour streptococcus hemolysins from the true microbial haemotoxins." The production of hemolyzing substances by various strains does not correlate with the pathogenicity for mice and rabbits.

M. S. MARSHALL.

IMMUNIZATION OF THE NEW-BORN WITH B C G. B. IAKHNIS, *Ann. de l'Inst. Pasteur* **41**:1045, 1927.

The Ukrainian Commission reports the results of their investigations thus far. Vaccination with B C G does not appear to exert any immediate influence on the state of health of the child, on the temperature, digestive organs, development, or resistance to exogenous or endogenous infections. Vaccinated children not exposed to tuberculosis often give a tuberculin reaction of medium intensity; those exposed more often show a marked reaction. The latter group probably are infected at an early age with virulent organisms. The Commission

considers the results encouraging, but conservatively states that all possible correlation should be made between the development, morbidity and mortality in nonimmunized children and in those who receive treatment.

M. S. MARSHALL.

ACTION OF SPECIFIC ANTIBODIES IN THE ORGANISM, IV. A. SPERANSKY, *Ann. de l'Inst. Pasteur* 41:1063, 1927.

One of the remarkable physiologic peculiarities of the central nervous system is that there exists somewhere a "hemato-encephalic" barrier, which is essentially a part of the defense mechanism. A great number of toxic substances are not arrested by this barrier; antibodies in the serum, however, do not ordinarily penetrate it. The author studies rabies, diphtheria, tetanus, dysentery, scarlet fever, measles and epidemic cerebrospinal meningitis. He concludes that for a general malady a toxin or virus must penetrate to the heart of the central nervous system, and considers the nature of diseases and manner of serum therapy from this point of view.

M. S. MARSHALL.

CONTRIBUTION TO THE STUDY OF LYSOZYMES. M. HEYMANS, *Arch. internat. de méd. expér.* 3:223, 1927.

This study is concerned with the distribution of microbes sensitive to lysozyme; the distribution of lysozyme in the various body fluids, and the examination of certain of its properties. There is more likelihood of finding organisms susceptible to lysozyme in the atmosphere than elsewhere. The ones isolated developed forms closely resembling sarcina. Lysozyme was found in egg-white and in the lacrimal secretions. The author was not able to detect it in blood serum, vitreous or aqueous humor or amniotic fluid. It is precipitated by ammonium sulphate and absorbed by animal-black. It is not destroyed by trypsin, alcohol, ether, chloroform, carbon-tetrachloride, and it is not soluble in these solutions. Lysozyme appears to behave like a ferment.

N. ENZER.

THE ISO-AGGLUTININS. N. G. COLLON, *Arch. internat. de méd. expér.* 3:237, 1927.

Three phases of iso-agglutination were investigated: The rôle of heredity in their transmission; their formation, and the formation of their antigens in the new-born, and their influence on pregnancy.

Statistical study confirmed the theory of hereditary transmission of blood groups, and Collon maintains that this fact may be made use of in medicolegal disputes. Iso-agglutinins are elaborated during intra-uterine life, but the iso-agglutinogens are formed after birth.

N. ENZER.

EFFECT OF BLOCKING THE RETICULO-ENDOTHELIAL SYSTEM ON NATURAL AND ACQUIRED IMMUNITY. M. G. COLLON, *Arch. internat. de méd. expér.* 3:273, 1927.

Blockage does not have any effect on the natural immunity of the guinea-pig, the dog and the hen. Complement reserve is not influenced in the rabbit twenty-four hours after the administration of the blocking substance. The elimination of foreign serum and the formation of precipitins continues when the rabbits are blocked with china ink and trypan blue. The simultaneous injection of two foreign serums and the quantity injected does not seem to modify the elimination of the heterologous serum. The animals blocked con-

tinue to form bacteria and blood agglutinins. The production of hemolysins and bacterial lysins in recurrent infections is not affected by blockage. The production of antitoxins was not inhibited. The only instance of successful blocking occurred when rabbits were injected with china ink. These failed to develop agglutinins for paratyphoid B.

N. ENZER.

BLOOD GROUPS IN NORTHERN ARGENTINA. L. MAZZA and J. FRANKE, *Prensa méd. Argent.* **14**:408, 1927.

No representatives of groups A and B were found among Argentine Indians and this fact is regarded as indicating that American natives were not of Asiatic origin.

THE IMMUNOLOGIC SIGNIFICANCE OF BACTERIAL LIPOIDS. R. KAWAI, *Centralbl. f. Bakteriologie* **102**:423, 1927.

Kawai concludes that the bacteriol lipoids per se do not have any direct immunizing property. Their union with the antigen proteins of bacteria, however, makes the latter more easily phagocytized and used. He then discusses the possible reasons for differences in toxicity of whole and defatted antigens.

PAUL R. CANNON.

THE TISSUE REACTION TO BACTERIA: IV. THE EFFECT OF ORGANISMS NON-PATHOGENIC FOR MAN IN THE SKIN OF GUINEA-PIGS: V. THE EFFECT OF CERTAIN ANIMAL STREPTOCOCCI IN THE SKIN OF RABBITS. H. DOLD, *Centralbl. f. Bakteriologie* **103**:321, 1927.

Dold continues his studies as to the effect of injecting various bacteria into the skin of rabbits and guinea-pigs and finds: (1) the strains of *B. prodigiosus*, *M. catarrhalis*, *Staphylococcus citreus*, *M. tetragenus* and *Sarcina* which he used gave in the skin of the guinea-pig an insignificant inflammatory reaction; (2) two strains of the Friedländer group gave a marked infiltrating effect with necrosis; (3) in the subtilis and mesentericus strains one had infiltrating and necrotizing properties, and (4) certain of the water vibrios caused edema, phlegmonous inflammation and death of the guinea-pig.

With the streptococci from horses, swine, sheep and dogs, he found the same three reaction types such as he described in his second and third communications.

PAUL R. CANNON.

THE DIAGNOSIS OF TYPHOID FEVER BY THE INTRADERMAL REACTION. P. A. ALISSOW and U. I. MOROSKIN, *Centralbl. f. Bakteriologie* **103**:332, 1927.

The authors autolyzed a twenty-four hour culture of typhoid bacilli for from three to five weeks at 37 C., added 0.25 per cent phenol and allowed it to stand at room temperature for the same period, after which the clear fluid was decanted, tested for sterility and then diluted until 0.1 cc.; when it was injected intracutaneously into a guinea-pig, it did not cause any reaction or only a slight reaction. This amount was then used for intracutaneous injections into human beings. In 104 cases which were clinically typhoid or paratyphoid fever, the intradermal test was positive in 82.6 per cent. In 158 cases not clinically typhoid, 5 gave positive intradermal reactions with negative Widal reaction. The authors conclude that the intradermal reaction is of the same value as the Widal, and is superior in that it is independent of laboratory facilities in the main.

PAUL R. CANNON.

THE DUST CELLS OF THE LUNGS AND THE HEART FAILURE CELLS: INTRODUCTION TO THE PROBLEM OF IMMUNITY. A. ALEXEIEFF, *Centralbl. f. Bakteriol.* **103**:390, 1927.

This paper, with two figures and one plate, deals with the problem of the origin of the heart failure cells. Alexeieff maintains that the heart failure cells are mesodermal and belong to the reticulo-endothelial system. He then discusses at length the clinical significance of these cells, the rôle of the reticulo-endothelial system with particular reference to immunity. Experimental work is not reported, most of the ideas being based on cytologic facts. Alexeieff thinks of the cells of the reticulo-endothelial system as functioning mainly through their liberation of lipases, directly and through the thrombocytes, which injure the lipoidal envelops of foreign cells (bacteria, etc.), and thus make them more susceptible to phagocytosis. He considers these lipases to have an amboceptor-like action, complement being a tryptic-like ferment. He considers agglutination as the first phase of the lipolytic effect, and illustrates it by the Rieckenberg phenomenon. In brief, he argues that the terms for the various antibodies should be abandoned, and that the immune reactions should be considered as due to the effects of various specific enzymes, the two most important, in his opinion, being lipases and proteases.

PAUL R. CANNON.

THE PERMEABILITY OF THE LIVING PERITONEUM FOR TOXINS, ANTIBODIES AND FOREIGN PROTEINS. DESIDER ENGEL, *Centralbl. f. Bakteriol.* **103**:423, 1927.

Engel injected horse serum, toxins and agglutinating serums subcutaneously in mice and guinea-pigs, and at certain intervals later, injected saline intraperitoneally. Withdrawal of this saline and appropriate testing revealed that the substances had passed into the peritoneal cavity. His observations indicate that the permeability for horse serum, hemolysins and agglutinins and diphtheria toxin corresponds more to that exhibited with acid dyes. Tetanus toxins and precipitins, which did not pass through readily, he feels act like basic dyes which also tend to be retained by cells before reaching the peritoneum.

PAUL R. CANNON.

BLOOD GROUPING IN A HEMOPHILIC FAMILY. ANDRÉAS KUBÁNYI, *Klin. Wchnschr.* **5**:321, 1926.

The studies indicating the heritable nature of blood groups suggests a possible relationship with hemophilia. A patient whose condition and family history indicate that he is hemophiliac, is found to belong to group 2 as do also his mother and sister. His healthy brothers belong to group 3.

INVESTIGATIONS OF THE BLOOD GROUPING IN THE HEMOPHILIC MAMPEL FAMILY OF HEIDELBERG. ANDRÉAS KUBÁNYI, *Klin. Wchnschr.* **6**:1517, 1927.

Investigations concerning the occurrence of hemophiliac persons in the Mampel family of Heidelberg, covering a period of more than 100 years, are briefly reviewed. A report of 1905 stated that of 207 members examined, 111 were men, and of these, 37 (33.33 per cent) were hemophiliac. In the present study of the blood grouping of thirty-seven members of this family (in four different branches), only groups 2 and 4 were found. Three of the four persons with hemophilia who were severely affected but survived belonged to group 4; no nonhemophilic man belonging to group 4 was found; and the daughters of

these families were all in group 2. The coincidence is noted that all the men who married into this family (so far as the study goes) belonged to either group 2 or group 4. Studies are planned for the children of the daughters in the present generation.

ETHEL B. PERRY.

IS THE SCHICK TEST A PRACTICAL MEASURE OF IMMUNIZATION AGAINST DIPHTHERIA? H. OPITZ, *Klin. Wchnschr.* 6:1701, 1927.

A single injection of toxin in the amount used with the Schick test stimulates antibodies. Therefore, the intracutaneous testing of diphtheria toxin is not suited for determining an immunization procedure. A further opportunity for error lies in the use of attenuated toxin solutions, which does not cause any skin reaction and therefore, may suggest an established immunity. Toxins for the Schick test should be titrated at the place where they are being used.

AUTHOR'S SUMMARY.

IS THERE A RELATION BETWEEN BLOOD GROUP AND SYPHILIS DISPOSITION AS WELL AS BETWEEN BLOOD GROUP AND THE SUCCESS OF SYPHILIS THERAPY? M. GUNDEL, *Klin. Wchnschr.* 6:1703, 1927.

There is no relationship between blood group and predisposition to syphilis. Changes of the blood group under the influence of infectious diseases and treatment for syphilis was not observed. Marked differences were noted in the four groups as regards the effect on the Wassermann reaction by the specific treatment. With blood groups A and O, the Wassermann reaction became negative much faster than with the groups AB and B. The same was noted with the Sachs-Georgi reaction. The author discusses whether these differences of the Wassermann reaction are due to an easier cure for syphilis in the group A and O, and if the more frequent occurrence of late syphilitic manifestations in the groups AB and B bears any relation to these observations. Further studies are needed to answer these questions.

AUTHOR'S SUMMARY.

TETANOSPASMIN AND TETANOLYSIN. G. C. REYMANN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 51:1, 1927.

Reymann describes further experiments with tetanus toxin. The tetanolysin is markedly weakened by filtration through a Berkefeld filter and by passage of air through it. Witte peptone gives stronger tetanolysin than does Martin peptone. There is no quantitative relationship between lysin and spasmin formation, but both are present in normal cultures.

PAUL R. CANNON.

IMMUNITY IN RELAPSING FEVER: 1. THE INFLUENCE OF THE RETICULO-ENDOTHELIAL SYSTEM. I. L. KRITSCHESKI and P. L. RUBINSTEIN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 51:27, 1927.

The authors have studied infection with *Sp. duttoni* in white mice. Subcutaneous injection of from 0.028 to 0.033 cc. of blood from an infected mouse into each of 183 mice gave a fatality rate of 3.83. Laparotomy, followed in twenty-four hours by the same procedure, gave a fatality rate of 4.25 per cent in ninety-four animals. Splenectomy, however, followed by the foregoing treatment, led to a high fatality rate, so that if done within three days after splenectomy, the fatality rate in 140 mice was 82.15 per cent. Later, compensatory mechanisms decreased the death rate so that seven days after splenectomy, only 15 per cent of forty animals died. Splenectomy plus blockade of the reticulo-

endothelial system by the injection of 0.5 cc. of a 5 per cent solution of iron saccharate in saline, followed by infection, gave a fatality rate of 90.47 per cent in thirty-eight mice tested. Blockade alone, in twenty-six animals, gave a fatality rate of 46.15 per cent. Partial splenectomy had slight effect on the usual course of recurrent infection. Transplantation of the spleen also did not have any material influence on the course of the infection in splenectomized mice. Consequently, the authors feel that they have, using adequate numbers of animals, established the predominant importance of the reticulo-endothelial system in immunity to a spirochetal infection.

PAUL R. CANNON.

THE RETICULO-ENDOTHELIAL SYSTEM IN RATS WITH RELAPSING FEVER. A. W. LISGUNOVA and A. P. BUTJAGINA, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:56, 1927.

The authors report the course of experimental recurrent fever infection in rats under various conditions. Splenectomy, followed within twenty-four hours by infection with *Sp. Duttoni*, led to fatality rate of 100 per cent in thirty-eight rats, the animals usually dying at the height of the first crisis, with enormous numbers of spirochetes in the blood. Blockade of the reticulo-endothelial system by the intravenous injection of 0.7 cc. of a 10 per cent iron saccharate solution per forty grams weight, followed by injection of the spirochetes, led to a fatality rate of 36.3 per cent in eleven rats. Laparotomy alone, followed by infection, gave a fatality rate of 4.54 per cent, with twenty-two rats. Hence, the authors conclude that in rats, the most important protective organ against relapsing fever is the spleen and the reticulo-endothelial system.

PAUL R. CANNON.

THE FORMATION OF LIPOID ANTIBODIES IN SYPHILITIC IMMUNE RABBITS. J. STEINFELD, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:73, 1927.

Steinfeld injected syphilitic immune rabbits with alcoholic extracts of rabbit kidney and swine serum and found a rapid and strong development of lipoid antibodies. A similar series, injected with alcoholic rabbit kidney extract alone, did not lead to the formation of lipoid antibodies. The intravenous injection of syphilitic immune rabbits with spirochetes from testicular chancres, did not give lipoid antibodies. The number of experiments, however, is too small, and further studies are necessary.

PAUL R. CANNON.

ANAPHYLACTIC SHOCK IN WHITE RATS. M. K. EBERT, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:79, 1927.

Ebert injected twenty-nine white rats with horse serum, using the Parker method (*J. Med. Research* **44**:263, 1924). Reinjection, usually from seven to nine days later, gave, in no case, anaphylactic shock, such as was seen by the Parkers. Injection of twenty rats with sheep's corpuscles led to similar results. The author demonstrated precipitins in the serum from the rats injected with horse serum and discusses the relationship of precipitin formation and anaphylaxis.

PAUL R. CANNON.

CERTAIN CONSTITUENT CELL PRODUCTS OF THE ACID-FASTS AND THEIR ANTIGENIC CHARACTER. A. KORFF-PETERSEN and W. LIESE, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:87, 1927.

The authors found that by acid hydrolysis in aqueous and alcoholic mediums, with cold and hot alcohol extraction followed by staining with various stain-

ing procedures, the chemical structure of true tubercle bacilli agreed with that of the nonpathogenic acid-fast. Lipoid extracts of the acid-fast bacilli react positively in complement-fixation tests. They are not specific for tubercle bacilli, however. Acid hydrolysis plus hot alcohol extraction give substances which are specific for the tubercle bacilli by the complement-fixation test. This is not the case when similar procedures are applied to the saprophytic acid-fast bacilli.

PAUL R. CANNON.

THE INFLUENCE OF THYROIDECTOMY ON ANAPHYLACTIC SHOCK. MOYER S. FLEISHER and C. M. WILHELMJ, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:115, 1927.

The writers find that thyroidectomy previous to sensitization markedly diminishes the percentage occurrence of lethal anaphylactic shock in guinea-pigs. This effect of thyroidectomy is not noted in rabbits, but there appears a change in the reaction of thyroidectomized rabbits following a second injection of antigen. The blood of thyroidectomized sensitized rabbits and guinea-pigs serves to passively sensitize normal guinea-pigs. Thyroidectomy does not appear to influence the production of anaphylactic antibodies or the sensitization of animals, but probably alters the general functional response of the shocked animal, following the second injection of the antigen.

PAUL R. CANNON.

THE INFLUENCE OF THYROIDECTOMY ON CHANGES OF THE SURFACE TENSION OF THE PLASMA IN ANAPHYLACTIC SHOCK. MOYER S. FLEISHER and C. M. WILHELMJ, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:126, 1927.

A fall in the surface tension of the plasma of animals in anaphylactic shock was found. In thyroidectomized guinea-pigs, the changes in surface tension of the plasma following a second injection of an antigen appears to be midway between the change noted in normal shocked animals and that noted when normal animals are for the first time injected intravenously with an antigen. While thyroidectomized animals do not respond in anaphylactic shock as do normal sensitized animals, they do show a somewhat similar reaction.

PAUL R. CANNON.

THE PRESENCE OF ANTIBODIES IN FROG'S BLOOD. L. SCHWARZMANN, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:139, 1927.

Schwarzmann found in normal frog's blood hemagglutinins and hemolysins against different erythrocytes. Immunization with erythrocytes of warm-blooded animals led to the formation of hemolysins. No thrombocytobarins were formed by immunization with trypanosomes. He concludes that cold-blooded animals also have a humoral mechanism of defense.

PAUL R. CANNON.

THE DISTRIBUTION OF HETEROGENETIC ANTIGENS IN THE ORGANISM AND THE INFLUENCE OF THEIR IMMUNIZING FUNCTION THROUGH OTHER ANTIGENS OF HIGHER SPECIFICITY. ERNST WITEBSKY, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:161, 1927.

Witebsky finds the Forsmann lipid, by the complement-fixation reaction, in alcoholic extracts of the blood cells of guinea-pigs and dogs, as well as from sheep kidney. Treatment of rabbits with guinea-pig erythrocyte or with alcoholic extracts of guinea-pig's corpuscles in combination with swine serum,

leads to the formation of antibodies which with complement cause hemolysis of guinea-pig's erythrocytes. Such serum does not contain any hemolysins for sheep's erythrocytes, but contain complement-fixing antibodies for alcoholic extracts of guinea-pig blood.

PAUL R. CANNON.

THE NATURE OF THE PROTEIN COMPONENT IN ANTIBODY FORMATION BY LIPOIDS.
ALBERT SIMEONS, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:193, 1927.

Injection of rabbits with a combination of lecithin and rabbit serum heated at 100 C. was as effective as the combination of lecithin and fresh rabbit serum in stimulating antibodies to lecithin. Parallel experiments with lecithin and swine serum led to similar results.

PAUL R. CANNON.

A NEW TYPE OF INHIBITION PHENOMENON IN AGGLUTINATION. LADISLAUS DETRE, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:205, 1927.

The author describes the observations of serums against *B. abortus* (Bang) which agglutinated to a dilution of from 1:20 to 1:30, after which there was a zone of inhibition until a dilution of from 1:150 to 1:1,000 was reached. He discusses the possible factors involved and describes the details of his experimentation.

PAUL R. CANNON.

PREVENTIVE INOCULATION AGAINST TUBERCULOSIS WITH CALMETTE'S B C G.
R. KRAUS, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **51**:230, 1927.

Kraus discusses the problem of immunity in tuberculosis and describes his experiments with the B C G. Contrary to Calmette's results, he finds that the organism possesses a certain virulence for animals with the production of definite tuberculous changes. These areas remain localized, however, and heal readily; he did not succeed in passing the infection from one guinea-pig to another one. Consequently, he feels that the cultivation of the B C G on bile mediums has definitely reduced its virulence, similarly to the virus fixé. The favorable results obtained by Calmette are due to the virulence of the B C G, rather than because it is avirulent.

PAUL R. CANNON.

A CLASSIFICATION OF CANCER PATIENTS ACCORDING TO THEIR BLOOD GROUPS AND SOME INVESTIGATIONS CONCERNING ISOHEMAGGLUTINATION. ERIK W. JOHANSEN, *Acta path. et microbiol. Scandinav.* **4**:175, 1927.

Among 383 patients with malignant tumors there was a higher percentage of groups A and B than among 533 healthy persons (Danes). This difference was accentuated by further classification according to sex and age, with the height of the increase in the group 2 percentage among women with uterine cancer. There was no indication in this great number of blood groupings of more than the four iso-agglutinative groups.

The iso-agglutinins were entirely contained in the precipitate obtained from plasma by the addition of an equal volume of saturated ammonium sulphate solution. Corpuscle shadows (stroma) centrifugalized from freshly laked corpuscles and washed several times in physiologic sodium chloride solution contained specific agglutinogens, but it could not be claimed that the agglutinable substance was contained only in the stroma.

GLOBULINS IN RELATION TO WASSERMANN AND SACHS-GEORGE REACTIONS. J. FORSSMAN, *Acta path. et microbiol. Scandinav.* 4:198, 1927.

The Wassermann reaction is independent of the globulins while the Sachs-Georgi reaction is dependent on the presence of globulins. The two reactions are distinct.

THE ISO-AGGLUTINABILITY OF HUMAN BLOOD PRESERVED IN DIFFERENT WAYS. LILLY SANDSTRÖM, *Acta path. et microbiol. Scandinav.* 4:260, 1927.

Human blood cells of groups A and B were tested with varying dilutions of serums of groups B and A, respectively, after preservation by different methods: salt solution suspension of cells from clot; salt solution suspension of citrated cells immediately after bleeding or only at time of use, citrated cells kept at 0 C. with fluid withdrawn, and citrated cells suspended in salt solution with 1 per cent formaldehyde. In general, there was beginning loss of agglutinability within two or three days, but cells in the formaldehyde-salt solution retained their agglutinability for from ten to twelve days in a usable degree.

EFFECT OF ROENTGEN RAYS ON ISOHEMAGGLUTINATION. T. MURAMATSEE, Japan *M. World* 7:287, 1927.

Roentgen rays may reduce iso-agglutination, but they change the blood group.

AN EXPERIMENTAL AUTOHEMOLYSIN IN THE RABBIT. M. NAMBA, Tohoku J. *Exper. Med.* 9:454, 1927.

By injecting emulsions of organs of guinea-pigs, horse or dog, autohemolysin is produced in one third of the rabbits so injected. This lysin is complex and is inactivated by heating to 50 C. The lysin is bound to the red corpuscles only when the temperature is under 7 C.; it exists in the plasma of the blood and acts in vivo on the homologous corpuscles on sufficient reduction of the temperature, but certain corpuscles are not susceptible to its action. The lysin is not identical with Forsmann's antibody.

Tumors

ON IMMUNITY OF FOWLS AGAINST THE CARREL INDOL TUMOR. H. B. ANDERVONT, *Am. J. Hyg.* 7:786, 1927.

Transplants of the Carrel indol tumor were capable of producing a growth within the combs of chickens. A certain percentage of these comb tumors regressed, and the fowls were immune to subsequent intramuscular implants of the indol tumor. They were also immune to subsequent implants of chicken tumor 1. Immunity was not established by the presence of tumor tissue alone, but its active growth followed by its regression was necessary.

AUTHOR'S SUMMARY.

AN INEFFECTUAL ATTEMPT TO CULTIVATE THE GLOVER ORGANISM FROM CARCINOMAS. JOHN A. KOLMER and others, *J. A. M. A.* 89:1868, 1927.

Culture were made from seventeen carcinoma tissues; no organism was found that resembled in the slightest degree that described by T. J. Glover.

THE BREAKDOWN OF HEREDITARY IMMUNITY TO A TRANSPLANTABLE TUMOR BY THE INTRODUCTION OF AN IRRITANT AGENT. ELIZABETH JONES, J. Cancer Research **10**:435, 1926.

Jones investigated the effect of an irritating agent in the production of susceptibility to an inoculable tumor in nonsusceptible strains of mice. As an irritant she used sterilized, nondyed, pure wool flannel. The experiments were conducted on black and albino mice. Both the black and the albino stocks have been used in numerous experiments as nonsusceptible controls. The animals were inoculated by the customary trocar method, the tissue being placed in the axillary region. The results obtained indicate a large percentage of positive results. On histologic examination and by inoculation of the "induced" tumors into different strains of susceptible and nonsusceptible mice it was evident that growth of the original tumor has been induced through the presence of the flannel, and that the neoplasms are not growth of the host tissue.

B. M. FRIED.

ON SYSTEMIC FACTORS IN THE GENESIS OF TAR CANCER. LEIV KREYBERG, Brit. J. Exper. Path. **8**:352, 1927.

White mice were painted with tar on one flank and thermocauterized on the opposite flank over a period of several months. Tumors developed in the painted areas in all except five of the fifty animals, and in the thermocauterized areas of eight of them. Forty control animals, cauterized but not tarred, did not develop a single tumor in these areas. Tar, through a systemic factor, influences the skin so that the incidence of tumors is increased following local insult.

S. D. SIMON.

RELATIVE p_H OF MAMMALIAN TISSUES AND THE POSSIBLE RÔLE IN TUMOR FORMATION. E. HARDE and P. HENRI, Ann. de l'Inst. Pasteur **41**:1022, 1927.

Determinations were made by the intravital use of brom cresol purple, phenol red and brom thymol blue. In mouse tumor, a $p_H < 6.6$ was noted with phenol red; p_H 6.0 with brom thymol blue, and a p_H from 5.8 to 6.2 with brom cresol purple. Similar results were noted with rat sarcoma. Embryonic white mice had a p_H of from 5.6 to 5.8; young healthy rats and mice, from 6.6 to 7.2; adult (4 to 6 months) healthy mice, from 7.4 to 7.8; and old healthy mice or carriers of tumors (16 to 18 months), from 7.0 to 7.2. The authors conclude that acidity is a favorable factor in the development of tumors.

M. S. MARSHALL.

SERODIAGNOSIS OF CANCER BY PRECIPITATION. C. MONDAIN, R. DOURIS and J. BECK, Ann. de l'Inst. Pasteur **41**:1097, 1927.

The authors consider the Botelho reaction to be a precipitation of albuminoid substances of the serum in acid medium by a nonspecific reacting precipitant; hence the reaction cannot be considered specific. The details of technic are given.

M. S. MARSHALL.

HYPERPLASIA AND SARCOMATOSIS OF THE LYMPH NODES. MARIO ARESU and ROSARIO SCALABRINO, Tumori **13**:307 and 403, 1927.

In an elaborate article which is accompanied by many photomicrographs, Aresu and Scalabrino give full details of three cases of lymphadenoma, eight cases of lymphosarcoma of Kundrat's type and thirteen cases of sarcoma of the lymph nodes. After a thorough discussion of the literature and of their

own cases, they arrive at the conclusion that the so-called lymphosarcoma which belongs to the group described by Kundrat is in reality lymphadenoma. These tumors are mostly aleukemic, sometimes subleukemic, but rarely leukemic. In comparison with the ordinary lymphadenoma, it is characterized by a greater tendency toward the production of less differentiated cell forms and a lesser tendency toward the development of adult lymphocytes.

The lack of differentiation which the proliferating tissues show varies from case to case. Sometimes the proliferation of the hemohistioblasts prevails, sometimes that of the lymphoblasts. The presence of these diverse elements gives the tissues a peculiar characteristic pleomorphism which varies from case to case and even in different lymph nodes in the same case. The lymphoma of Kundrat's type might therefore be called lymphadenoma of anaplastic type, while the ordinary ones are of the metaplastic type. Some of these growths may even contain megakaryocytes and Sternberg cells. The authors believe that the true sarcoma of the lymph nodes can be distinguished clearly from these two types of lymphadenoma, not so much by their clinical symptoms as by their histologic appearance.

W. OPHÜLS.

THE STRUCTURE OF CONNECTIVE TISSUE TUMOR CELLS IN MAN. H. CASTRÉN, Arb. a. d. path. Inst. d. Univ. Helsingfors. 4:241, 1926 (new series).

The operative material included three fibromas, three fibrosarcomas, nine spindle cell sarcomas and six polymorphocellular sarcomas. Three types of cells were noted in these. The majority were spindle-shaped like fibroblasts; a regressive type was represented by small rounded-off forms and a progressive type by variously shaped large cells containing one or more nuclei. Tumor cells exhibit variations in size, shape, chromatin content of the nucleus, dimensions of the nucleoli, cytoplasm structure and centrosome position not found in resting cells. In inflammatory reactions cells have an orderly succession of events in fibroblast to giant cell formation, but such evolution is much less a part of growth in tumors. The greatest similarity was found between spindle-shaped tumor cells and resting or slightly stimulated fibroblasts. There was a certain superficial similarity between the sarcoma cells of regressive type and rounded off fibroblasts such as epithelioid cells of tuberculosis.

GEORGE RUKSTINAT.

CHARACTERISTIC PROPERTIES OF CARCINOMA CELLS IN VITRO. A. FISCHER, Klin. Wchnschr. 7:6, 1928.

One of the reasons that carcinoma cells proliferate in the tissues is that they are able to build up their cell constituents from substances in serum and from substances of the normal cells with which they come in contact.

E. F. HIRSCH.

SPONTANEOUS HEALING OF A TERATOMA OF THE TESTIS. P. PRYM, Virchows Arch. f. path. Anat. 265:239, 1927.

Proof of the spontaneous regression and complete healing of malignant neoplasms is difficult to establish. Prym reports a patient who died at the age of 51, with a large retroperitoneal tumor mass and metastases of the urinary bladder, left kidney, liver and lungs. The tumor tissue was cellular and contained giant cells and syncytial masses which led Prym to conclude that the tumor was a chorio-epithelioma. The right testis, which was slightly decreased

in size, contained a pale, poorly defined, cherry-sized nodule. Microscopically, this was composed of dense fibrous tissue, which was partly necrotic. At the periphery of the nodule, connective tissue with newly formed blood vessels radiated out into the testis, the tubules of which were compressed and hyalinized. Tumor elements could not be seen in the nodule itself or in the surrounding tissue. Prym concludes that the testicular mass was a teratoma which had led to metastasis but which had itself undergone complete local regression.

O. T. SCHULTZ.

Medicolegal Pathology

SUBARACHNOID HEMORRHAGE FROM MEDICOLEGAL POINT OF VIEW. W. MUNCK, *J. Nerv and Ment. Dis.* **65**:484, 1927.

Isolated subarachnoid hemorrhage can be the cause of sudden death. Nine such cases are on record. In cases of this type, it is often extremely difficult to determine whether the hemorrhages are spontaneous or of traumatic origin, as the pathologic-anatomic picture in the two cases can be perfectly alike, both after rather large injuries and small traumatisms.

ZINC STEARATE INSUFFLATION. E. D. ANDERSON and E. H. HILBERT, *Minnesota Med.* **10**:276, 1927.

Eight cases of aspiration of zinc stearate are reported by Anderson and Hilbert. In many instances only the larynx is involved; the cases are not fatal and are of rather short duration. If the zinc stearate reaches the bronchi, it causes a severe bronchitis which may develop into a bronchopneumonia. If the powder reaches the lung tissue, it may cause a severe bronchopneumonia. The symptoms arising from aspiration of zinc stearate are probably due to both the mechanical and the toxic effects of the powder.

TRAUMATIC LACERATION OF THE RIGHT LUNG WITHOUT FRACTURED RIBS. M. DÉTIS, *Ann. de méd. lég.* **7**:46, 1927.

A young man fell from the seat of a horse-drawn vehicle when it collided with a truck, landing in front of a wheel. He was pushed along on his right side by the wheel for some distance, and sustained severe bruises, dislocation of the shoulder, comminuted fractures of the scapula and dislocation of the distal end of the clavicle, all on the right side. He was taken immediately to the hospital in a condition of severe shock, and died about an hour later.

All the lobes of the right lung were deeply torn by a vertical tear near the spine; the liver was bruised. It was assumed that in order to offer resistance to an expected crushing, the lungs were distended with air, the diaphragm and other respiratory muscles were held rigid and the glottis was closed. Then the pressure which did occur on the thorax, although it was not great enough to break any ribs or the sternum, nevertheless compressed the thorax enough to burst open the distended right lung.

E. R. LE COUNT.

MIDDLE OCCIPITAL FOSSA. M. COSTEDOAT, *Ann. de méd. lég.* **7**:73, 1927.

Asymmetrically placed depressions of the inner surface of the occipital bone midway between those on each side for the cerebellar hemispheres, have long been known as the middle or median occipital fossa. It is 1 or 2 inches (2.5 or 5 cm.) in diameter and lies between the back edge of the foramen

magnum and the torcular boss. It is not always present, and this inconstancy has been the subject of considerable discussion among anthropologic criminologists, ever since Lombroso advocated a greater frequency of the middle fossa in the skulls of criminals and associated it with overbalanced emotions and a larger middle lobe (vermis) of the cerebellum.

Such views have been vigorously disputed from time to time, and this study by Costedoat is a contribution to the controversy. Because he found this middle fossa well developed in the craniums of three of six executed criminals, an unusually high ratio, he was led to study collections of skulls in the Museums of Legal Medicine and Normal Anatomy at Lyon. Among 173 craniums of persons abnormal mentally, only seven had a middle fossa; three of these, however, were those of assassins. Among ninety craniums of normal persons, he found fifteen middle fossas. He failed to find any relation between the presence of middle occipital fossas and the general shape of the skulls, such as brachycephalism, dolichocephalism, etc., and supports a contention previously advanced that these median occipital fossas are due to anomalous arrangements of the dural sinuses which converge there. He suggests, in conclusion, the need of examining the dural sinuses in criminals as well as in others, since the discussion has centered chiefly about the conformation of carefully prepared dry craniums.

E. R. LE COUNT.

DEATH FROM ELECTRIC SHOCK WITH AN ALTERNATING CURRENT OF HIGH VOLTAGE;
NECROPSY. PAUL MULLER, *Ann. de méd. lég.* 7:176, 1927.

Subcutaneous hemorrhages of the right temple and left upper eyelid, with a burn of one hand, were the external injuries of a man who fell to a cement floor when shocked with an alternating current of 30,000 volts. He was somnolent, with a slow pulse rate of from 48 to 55, and there was blood in the spinal fluid, some deafness in both ears, a positive Kernig sign and rigidity of the neck and trunk. These symptoms lasted several days and in the disappearance of somnolence an impaired mentality became evident. Apparently, the psychosis was of considerable duration and possibly was permanent. The report fails to consider that some of the symptoms may have resulted from the fall.

E. R. LE COUNT.

IDENTIFICATION OF HUMAN BLOOD SPOTS. H. DIACONO, *Arch. d. Inst. Pasteur de l'Afrique du Nord.* 16:302, 1927.

The author, stating that the method of deviation of complement for the identification of human blood tends to supplant precipitin methods, gives his method and experimental observations. He finds the method sensitive, specific and satisfactory.

M. S. MARSHALL.

THE FORENSIC IMPORTANCE OF THE MICROSCOPIC EXAMINATION OF THE LUNGS OF
INFANTS DYING AT OR ABOUT THE TIME OF BIRTH. J. OLBRYCHT, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:529, 1927.

The length of the femurs, characteristics of meconium in the bowel and microscopic examination of the lungs served to demonstrate live birth at term of a child whose body was extensively burned to conceal murder by the mother. The outside of the lungs was cooked and gray for from 2 to 7 mm., but in many deeper places the alveoli were found well distended and the bronchioles circular

in place of the stellate fetal form from infolding of the lining. Many experiments were made by burning and partly cooking fetal human and bovine lungs into which it was definitely known air had never entered by respiration; such lungs were then microscopically examined in many places. Olbrycht also refers to results of the histologic study of the lungs in the routine examination of 188 fetuses and new-born infants.

From such studies the conclusion is expressed that, by and large, microscopic examination of the lungs if properly done so that the condition in many parts of both lungs is ascertained, affords the best means of demonstrating that respiration occurred. Postmortem gas production produces cavities in the interstitial septums, and superficial respirations followed by death causes distention of only certain portions. Other tests are not altogether deprecated, but this "histologic test" is the most trustworthy. It should be used in conjunction with microscopic examination of meconium, and whatever fluid there is in the lungs, also with the time honored hydrostatic tests.

E. R. LE COUNT.

THE MEDICO-LEGAL SIGNIFICANCE OF PACHYMEMINGITIS HEMORRHAGICA INTERNA.
M. KERNBACH and V. FISI, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 9:580, 1927.

Subdural hemorrhage covering the left parietal and temporal lobes and thrombosis of a cerebral vein, a subependymal hemorrhage and minute hemorrhages in the kidneys were found in an infant, aged 1½ years, who died unexpectedly. The changes were attributed to infection, but this is conjectured.

E. R. LE COUNT.

CONSTITUTIONAL PECULIARITIES OF THE BLOOD WITH SPECIAL REFERENCE TO THE QUESTION OF PATERNITY. OLUF THOMSEN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 10:1, 1927.

After a thorough review of the facts at hand concerning the inheritance of the factors that determine the blood groups, Thomsen reaches the conclusion that the hypothesis of three allelomorphs (Bernstein, Fukuhara, Enyder) is the most acceptable at this time.

HOW TO OBTAIN POTENT SPECIFIC ANTISERUM FOR FORENSIC DIAGNOSIS OF BLOOD.
G. BLUMENTHAL, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 10:17, 1927.

It is recommended first, that 1, 2 and 3 cc. of the foreign serum be injected into rabbits intravenously and successively on three consecutive days and, secondly, that 5 cc. of serum be injected intraperitoneally from eighteen to twenty days after these preliminary injections.

UNUSUAL MEDICOLEGAL EXPERIENCES: VOLUNTARY STRIPPING OUT OF COLON; INJURIES TO HEAD AND FEET IN HANGING; LATE CEREBRAL HEMORRHAGE FOLLOWING BLOW ON HEAD. ALEX SCHACKWITZ, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 10:31, 1927.

Following prolapse of the rectum due to jumping from the top of a wall, a boy, aged 14 years, pulled out the lining layers of almost the entire colon while at stool, thinking they had to do with some foreign body. It is of especial interest that he did not experience pain (*Arch. Path.* 3:1068 [June] 1927). Death occurred twelve hours later on the operating table.

Because of the wounds of the head and feet of the body of a man found hanging in a small workshop, the authorities at first thought a murder had been committed. It was subsequently decided that the injuries were sustained during convulsions which occurred during a suicidal hanging.

A youth, aged 19, died six days after receiving a blow on the head. There was no fracture of the skull. In the left cerebral hemisphere under the scalp wound, and mainly in the white substance, a hemorrhage was found. There was only a little blood free in the leptomeninges. On the day after the injury the man worked as usual, and it was not until the afternoon of the following day that the first symptoms developed without reason in form of speech difficulty and slowly developing hemiplegia. Operation was not performed.

E. R. LE COUNT.

BROADSIDE BULLET WOUNDS OF THE CRANIUM. NIPPE, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **10**:54, 1927.

Glancing from objects encountered in transit, bullets sometimes continue their course whirling end over end. One of the bullets in the cases reported was interrupted by a fence post, the other reflected from the surface of water or from some unascertained object in the water. The wounds of entrance they made in the cranium matched the profile of the bullets, oblong holes rounded at one end and square at the other. The wounds of the brain made by such bullet posses every feature of missiles with their speed about spent (*ARCH. PATH.* **3**:1067 [June] 1927).

E. R. LE COUNT.

ATTEMPTED INFANTICIDE; HEALED NEEDLE WOUND OF THE BRAIN. KURT HAUN, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **10**:58, 1927.

Remains of a needle were found in the brain of a man, aged 70 years. It had been inserted through the front fontanel the most ventral part of the left lateral ventricle and into the corpus striatum. The bone opposite its path was unchanged having developed subsequent to the injury. The dura had a minute polyp-shaped projection from its inner surface extending into the funnel-shaped opening of the wound in the brain in which the end of the needle lay. The brain tissue was heavily pigmented with iron, and an excellent roentgenograph was secured. The explanation was rather difficult because the brain had been kept in liquor formaldehydi eighteen years before the histologic examination was made. It was learned that the man was born out of wedlock.

E. R. LE COUNT.

LONGITUDINAL TEARS OF THE COMMON CAROTID ARTERIES. K. BÖHMER, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **10**:175, 1927.

In the carotid artery of a woman who committed suicide by hanging and in that of a man who was killed by a falling heavy iron plate, either entirely or partly lengthwise tears were found. In one vessel the wall was slightly diseased. The tears were of the innermost parts of the wall and of interest because of the great rarity of lengthwise lacerations. Transverse tears, on the contrary, are found in these arteries in from 5 to 14 per cent of the bodies of all persons strangled to death. It is possible that the longitudinal tears are produced by a folding inward of the artery wall when the neck is compressed.

E. R. LE COUNT.

HIDDEN TRAUMATIC TEARS OF NORMAL BASILAR ARTERIES. P. FRAENCKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:193, 1927.

The blood in and about the leptomeninges of the base of the brain was carefully washed away during many days by a gentle stream of water. This resulted in the discovery of a minute tear in the basilar artery. The bleeding followed a fight during which the head of the deceased was struck many times. One other similar rupture from trauma of the basilar artery has been reported. Both occurred in young men, and each tear was on one side of healthy vessels. It is suggested that unusual engorgement of the artery occurs, and that by the external violence the vessel is repeatedly flattened between the pons and clivus.

E. R. LE COUNT.

RUPTURE OF THE AORTA FOLLOWING BULLET WOUNDS. C. GORONEY, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:235, 1927.

Emboli of fat were found in the vaso vasorum of an aortic wall close to an extensive transverse tear located the width of a hand above a bullet path across the chest. Death occurred twenty minutes after the shooting. It was believed that the fat came from subcutaneous tissues and marrow of ribs in the bullet path. Emboli of fat were present in the lungs and other organs.

E. R. LE COUNT.

DETECTION OF MURDER IN DISMEMBERED BODIES. A. HABERDA, Deutsche Ztschr. f. d. ges. gerichtl. Med. **10**:242, 1927.

A detailed account is given of a man's attempt to drop portions of the body of his wife, which he had cut up, into the Danube River in Vienna in 1926. He was caught and he confessed. Other similar occurrences in Vienna are related, with reference to the methods employed in dismembering bodies, the difficulties encountered in demonstrating evidence of crime from an examination of such bodies or from such parts as are recovered and the mistakes easily made in connection with parts of bodies from dissecting rooms which are carelessly discarded and found in ash heaps, garbage dumps, etc.

E. R. LE COUNT.

DROWNING IN CONSEQUENCE OF PERFORATION OF THE EAR-DRUM. E. SCHLITTLER, Schweiz. med. Wchnschr. **57**:561, 1927. PERFORATION OF THE EAR-DRUM AS THE CAUSE OF DROWNING WHILE SWIMMING. FRANZ BRUCK, München. med. Wchnschr. **74**:897, 1927.

In the article by Schlittler the literature bearing on the question of drowning as a consequence of perforation of the ear-drum is reviewed, and the manner of examining the ears in suspected cases is considered in detail. It appears that a certain Swiss accident insurance company requires a careful examination of the ears in all cases of sudden death in water. It is pointed out that on account of the forensic importance of such cases it is extremely desirable that the pathologist and otologist cooperate closely. While in the large majority of possible deaths under these conditions perforation of the drum as the result of otitis had probably occurred, it is also to be borne in mind that rupture of the drum may result suddenly from falling into water. In the cases in question death is supposed to result as the consequence of disturbances in equilibrium from the entrance into the inner ear of water, resulting in disorientation. In examining the ears of the drowned persons, the question whether the drum

may have been destroyed by decomposition after death must be considered with great care, and Schlittler discussed this side of the problem in considerable detail.

BLOOD GROUPING IN FORENSIC MEDICINE. K. MEIXNER, *Wein. Klin. Wchnschr.* **40**:206, 1927.

In the discussion of Meixner's paper, Werkgartner states that in seventy-nine instances of cases of questionable paternity, studied by means of blood grouping, there were twelve cases in which the results indicated that the accused could not be the parent.

THE PROSPECTIVE RESULTS OF SEROLOGIC EXAMINATION OF PARENTS. F. Schiff, *Arztl. Sachverst.-Zeit.* **33**:49, 1927.

The definite exclusion of paternity is possible only in considerably less than 25 per cent of the cases. In 16.7 per cent of the cases in which the accused is not the father it is possible to exclude his paternity. In 137 cases paternity was excluded on the basis of blood grouping in 16, that is, in 11.7 per cent.

Technical

THE DETERMINATION OF THE SURFACE AREA OF WOMEN AND ITS USE IN EXPRESSING BASAL METABOLIC RATE. H. S. BRADFIELD, *Am. J. Physiol.* **82**:570, 1927.

Direct measurements of surface area by means of the surface integrator were made of forty-seven young women taken at random from university classes, and the observations obtained in this way were compared with the results obtained by calculation by the DuBois linear, the Woerner linear and the DuBois height-weight formulas. They were found to average the same as those obtained by the Woerner linear formula, being about 6 per cent below those of the DuBois linear, and nearly 2 per cent below those of the DuBois height-weight formulas. That the latter deviations are not without effect was shown by determinations of the basal metabolism, made repeatedly on sixteen of the subjects, which showed about 2 per cent greater deviation from the Aub-DuBois standards than from the Harris-Benedict or the Dreyer standards, when the DuBois height-weight formula was used to obtain surface area. With area determined by the integrator, approximately uniform deviation from all the standards was found.

It was found that the average basal metabolism was about 6 per cent below that predicted by all the standards used, and agreed with that predicted by Krogh. So that for accurate determination of this, the Krogh modification of the Aub-DuBois standards should be used, and a correction of plus 2 per cent should be made for surface area as determined by the DuBois height-weight formula.

H. E. EGGERS.

BLOOD BILIRUBIN. F. S. PERKIN, *Arch. Int. Med.* **40**:195, 1927.

The normal range was from 0.5 to 3.5 mg. per thousand cubic centimeters of blood. The effect of race and sex was not apparent and that of pigmentation was slight. Specimens from fasting subjects gave slightly lower results. It is of considerable value in patients receiving arsenical preparations as it gives the earliest possible indication of damage to the liver. In cases of disease of the liver, important information is often given, but the type of

reaction must not be entirely relied on as a means of diagnosis. Characteristically, there is no discernible effect in cases of cholecystitis and cholelithiasis without obstruction, twenty cases giving results within normal range, with one exception. The bilirubin is a valuable adjunct to the diagnosis and prognosis in diseases of the blood and blood-forming organs. The technic is as follows: To 2 cc. of oxalated plasma is added 2 cc. of diazo reagent, freshly prepared. After from two to three minutes, 5 cc. of 95 per cent alcohol and 2 cc. of saturated solution of ammonium sulphate are added. The solution is centrifugalized after shaking. The supernatant fluid is carefully drawn off and compared in a colorimeter, preferably of the Du Bosq type as more accurate, or in a Hellige colorimeter, with the standard solution described in the following. The result is multiplied by 4, none of the azobilirubin being dissolved in the ammonium sulphate, and expressed in milligram per thousand cubic centimeters of blood. The use of plasma instead of serum obviates to a great extent the occurrence of hemolysis, which interferes with the reaction and also gives a cloudy supernatant fluid. Even with the use of oxalated blood, early centrifugalizing is advisable although not absolutely necessary. The standard is made by dissolving 2.161 Gm. of anhydrous cobalt sulphate in 100 cc. of distilled water. The salt must be absolutely anhydrous and chemically pure, and when possible the solution should be checked against pure bilirubin. This standard gives a color equivalent to that given by 5 mg. of bilirubin per thousand cubic centimeters of blood, which constituted the old van den Bergh "unit." Various strengths of the aforementioned standard may be prepared for convenience in reading higher values of the unknown. When dilution of the unknown is necessary, 65 per cent alcohol should be used. This standard is permanent if kept in the dark.

S. A. LEVINSON.

METHOD FOR OBTAINING MATERIAL BY PUNCTURE OF LYMPH NODES. C. E. FORKNER, *Arch. Int. Med.* **40**:532 and 647, 1927.

Puncture of lymph nodes by means of a hollow needle through which a dental broach is passed is an efficient method for obtaining material for study. Such material can be studied by supravital methods, dark-field examination and fixed stains.

THE ELECTROMETRIC DETERMINATION OF IRON IN BLOOD. J. F. KING and F. H. HOWARD, *J. Biol. Chem.* **75**:27, 1927.

The proposed method is intended, principally, for application to research, when a somewhat greater precision is required than may be secured by existing colorimetric methods.

ARTHUR LOCKE.

THE MICRO-ESTIMATION OF PHOSPHATE AND CALCIUM IN PUS, PLASMA AND SPINAL FLUID. T. KUTTNER and H. E. COHEN, *J. Biol. Chem.* **75**:517, 1927.

An improved method is suggested for the colorimetric estimation of calcium and phosphorus. The method is based on the usual conversion of phosphate (e. g. calcium phosphate) into phosphomolybdic acid with subsequent reduction of the latter to a deeply colored complex the concentration of which can be determined colorimetrically, under controlled conditions. The new features appear to be: (1) an improvement in apparatus, (2) a more rapid and greater development of color and (3) a consequent increased sensitivity, permitting the use of smaller amounts of sample.

ARTHUR LOCKE.

ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN PHYSIOLOGICAL FLUIDS. M. C. REINHARD, *J. General Physiol.* **11**:1, 1927.

This article is principally an account of the use of the Hilger quartz photometer, with graphs illustrating the ultraviolet absorption spectrums of bile, saliva, pericardial fluid, urine, blood albumin, pseudoglobulin, euglobulin, blood serum and hemoglobin.

H. E. EGGERS.

WASSERMANN REACTION IN CEREBROSPINAL FLUIDS CONTAINING BLOOD. ALVIN G. FOORD and MARJORIE BAUCKUS, *J. Lab. & Clin. Med.* **8**:270, 1927.

It has been demonstrated that only very small amounts of Wassermann-positive blood need be introduced into normal cerebrospinal fluid to impart to the latter a positive Wassermann reaction, this being due to the fact that the test conducted with cerebrospinal fluid is done with relatively large amounts of fluid (ten times the usual serum amounts in most technics), and also because the usual four plus Wassermann serums are usually much stronger than four plus. In examining cerebrospinal fluids from patients showing a positive blood Wassermann reaction, we strongly advise against the use of fluids containing traumatic blood in grossly visible amounts. Negative reactions are as reliable as in those not containing blood, but a positive reaction may be due either to neurosyphilitic disease or to the contained blood.

AUTHORS' SUMMARY.

A PRACTICAL TECHNIC IN THE PREPARATION OF SMEARS FOR THE EXAMINATION OF TUBERCLE BACILLI. L. T. BLACK, *J. Lab. & Clin. Med.* **8**:287, 1927.

The sputum is placed in a bottle or container and whipped for one minute with a wooden applicator around the end of which a piece of cotton has been wrapped. The tubercle bacilli present in the sputum will become adherent to the cotton. The cotton-wrapped end of the applicator is then drawn once lightly and quickly across the slide, leaving a thin smear in which the tubercle bacilli are distributed homogeneously. This method is recommended as highly valuable.

DECALCIFICATION OF BONE BY MAGNESIUM CITRATE. B. KRAMER and R. G. SHIPLEY, *Science* **66**:485, 1927.

Dissolve 80 Gm. of citric acid in 100 cc. of hot water. Add 4 Gm. of magnesium oxide and stir until dissolved. Cool, and add 100 cc. of ammonium hydroxide (density 0.90). Dilute to 300 cc., let stand twenty-four hours and filter. (If the magnesium oxide contains much carbonate, it should be freshly ignited.) The solution remains clear for some time and on standing, more rapidly after agitation, crystals of ammonium magnesium phosphate make their appearance.

Titrate with fifth normal hydrochloric acid to a reaction of approximately pH 7 to 7.6 and add an equal volume of distilled water.

This fluid is efficient in softening bone after it has undergone the action of any of the common fixing agents, but it is perhaps better to fix and harden the specimen in formalin. The latter must be well washed out from the tissue, first in running water for from twelve to twenty-four hours according to the size of the specimen, and then in two or three changes of distilled water. The citrate solution should be changed fairly frequently, since it will otherwise dissolve the calcium salts to saturation. It has seemed best to replace the solution every other day. Decalcification proceeds relatively slowly as

compared with solutions of the strong acids such as hydrochloric or nitric, but it is much more rapid than Muller's fluid, picric or chromo-aceto-osmic acid, for example. The rib of a dog split through the center is freed from lime salts by this solution in about fifteen days. Swelling of the tissues is not induced by the fluid, and there is no apparent shrinkage of such cells as those of the bone marrow. Stains are taken up without difficulty. Unlike Muller's fluid, magnesium citrate allows decalcification to go on to completion and removes all possibility of distinguishing the osteoid tissue from bone which in life contained deposits of lime.

MODIFICATION OF THE SPIROCHETE IMPREGNATION METHOD OF FONTANA-TRIBON-DEAU. W. L. YAKIMOFF, *Centralbl. f. Bakteriologie*. **102**:89, 1927.

The purpose of this modification is to simplify the Fontana-Tribondeau method and consists in using a solution of glacial acetic acid, 2 Gm.; phenol crystals, 2 Gm.; formalin, 2 Gm.; tannin, 5 Gm.; alcohol 50 cc. and distilled water, 40 cc. A little of this is poured into a test-tube, heated to boiling and poured on the air-dried smear of spirochetes. It is then washed with water and the usual impregnation with silver nitrate (5 per cent) solution is done.

PAUL R. CANNON.

THE HOHN METHOD FOR THE CULTIVATION OF THE TUBERCLE BACILLUS. G. SCHRADER, *Centralbl. f. Bakteriologie*. **102**:163, 1927.

Schrader finds the Hohn method (*Centralbl. f. Bakteriologie*, I, O **98**:460, 1926) of great value in the cultivation of tubercle bacilli. The main feature of this method is the preliminary treatment of the suspected material with from 10 to 12 per cent sulphuric acid, in the proportions of 10 cc. to from 1 to 2 cc. of material to be tested, for twenty minutes; this is followed by centrifugalization and streaking of the sediment on Lubenau's medium.

PAUL R. CANNON.

THE CULTIVATION OF THE TUBERCLE BACILLUS IN THE DIAGNOSIS OF TUBERCULOSIS. ERIKA HERRMANN, *Centralbl. f. Bakteriologie*. **102**:169, 1927.

Herrmann considers the antiformin method superior to the sulphuric acid method, while he finds egg mediums best for cultivation of the tubercle bacilli.

PAUL R. CANNON.

A METHOD OF OXIDASE STAINING. H. EPSTEIN, *Centralbl. f. Bakteriologie*. **103**:329, 1927.

Epstein's method is as follows:

1. Fixation of blood smear, preferably fresh and at most not older than forty-eight hours, for three minutes in a mixture of alcohol (95 per cent) 90; solution of formaldehyde (40 per cent) 10.
2. Washing with distilled water (from fifteen to twenty seconds).
3. Pouring on a solution of alcohol, U. S. P., 42 cc.; alpha naphthol, 1; solution of hydrogen peroxide, 0.2; water to make 100 cc., for three minutes.
4. Washing with distilled water.
5. Stain with lithium citrate-toluidine blue solution. Toluidine blue 1; lithium citrate, 1; distilled water, 100 for fifteen minutes.
6. Washing in distilled water for one second.
7. Washing in 1 per cent tannin solution for one second.
8. Drying with filter paper.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 8, 1927

DAVID MARINE, *President, in the Chair*

INTRACRANIAL ANEURYSMS. BENJAMIN SHORE.

This paper will appear in full in the ARCHIVES OF PATHOLOGY.

DISCUSSION

ALFRED PLAUT: How was the specimen prepared?

BENJAMIN SHORE: The brain was hardened in formalin. The arteries were injected with formalin in the intact brain. Sections for microscopic study were taken from the cerebellar cortex and the brain stem. The arteries were dissected from the remainder by means of a stream of water and glass rods. It was a purely formalin preparation.

MAURICE PACKARD: I think Dr. Shore is unduly pessimistic as far as the diagnosis is concerned. In 1924, Zabriskie and I read a paper before the Neurological Section of the American Medical Association, wherein we described four cases of ruptured intracranial aneurysm in which the diagnosis was made before death. Since that time we have seen a few more cases at Gouverneur Hospital, and in some of these cases, I believe three or four, the interns made the diagnosis. The particular things that we noted about the cases were as follows: All of the patients suffered from an apoplectic shock, but that they were never absolutely comatose, for, although unconscious, we could arouse them from their stupor. They have other symptoms due to various nerve involvements, which may be due to the pressure of a large aneurysm, or to focal edema, which invariably follows irritation of the meninges by the extravasated blood. Accompanying this, there is meningism with its associated symptoms. Again blood is persistently present, as shown by spinal puncture; the spinal fluid may vary from bright red to yellowish, and there may not be any clots. If these signs and symptoms are present, one may be fairly certain that one is dealing with a leak of one of the basal arteries.

We have followed four cases to autopsy. In a number of cases in which we made the diagnosis, it was not confirmed at autopsy.

THE POTASSIUM AND CALCIUM CONTENT OF AND DISTRIBUTION IN NORMAL TISSUES. G. L. ROHDENBURG and J. GEIGER.

The original method for demonstrating potassium and calcium in the tissues as published by MacCallum was modified to permit permanent sections. Studies of the normal tissues showed that the largest amounts of potassium were found in (a) those tissues in which physiologic activity was at the highest point, namely, in the pancreas and in the lactating breast; (b) where replacement of cells was occurring most often, namely, in the basal layer of the surface epithelium. The ovum was found to contain large amounts of potash, while potash was not found in the sperm. Peculiar concentrations of potash were found in the gastro-intestinal tract, in the suprarenals and in certain areas of the brain.

The calcium distribution was most marked in the regions of the body in which repair is most frequently associated with calcification. Characteristic deposits of calcium were found in the motor areas of the brain, in certain

motor fibers and in the spinal cord. The sperm head was shown to contain a large amount of calcium.

DISCUSSION

F. H. DIETERICH: As I understand it, those cells that show the most senescence show the most calcium. Could it possibly be due to the fact that calcium has something to do with senescence? In other words, does one find more calcium in older animals of the same species than in the younger members?

LOUIS GROSS: I should like to ask Dr. Rohdenburg whether he has made a comparison of the quantity of calcium and potassium as demonstrated by his histochemical method with that determined by chemical quantitative estimations in these organs.

GEORGE L. ROHDENBURG: In the present work that comparison has not been made, but in work reported about five or six years ago, in which the question of malignant tissues was studied, it was. In comparing two different tumors we made histochemical examinations and photomicrographs and cut out every black dot for four or five photomicrographs. We weighed the tumors, and came to the conclusion that tumor A contained half, once, twice, or five times as much as tumor B. We then checked up tumor A and B by chemical analysis, and came to the same conclusion. If histochemical examination showed that one tissue contained more than the other, chemical examination showed the same result. Of course, this is not even a remotely accurate method. One has only relative comparisons, but these comparisons check up with the chemical examination.

In answer to Dr. Dieterich's question, I stated before that one man's guess is as good as another's. I do not know whether calcium has anything to do with senescence or not. We have simply reported what we have seen. We are following the investigation further in pathologic conditions, which will probably give us some sort of clue concerning the meaning of these facts.

A CASE OF CAVERNOUS TRANSFORMATION OF THE PORTAL VEIN. PAUL KLEMPERER.

A case of cavernous transformation of the portal vein after chronic thrombosis was reported. The pathogenesis of the condition and its relation to Banti's disease were discussed. A complete report will be published at a later date.

DISCUSSION

NATHAN ROSENTHAL: I have followed this case, as well as many others which have been diagnosed by removal and histologic examination of the spleen as Banti's disease. According to our observations, we can divide them into three distinct groups. One is the group just described, the thrombocythemic group, of which I have followed four cases. All of the patients have died after operation. The second group is the so-called thrombocytopenic group, and the patients usually have a hemorrhagic diathesis. They may not show hemorrhages in the skin, but may have nosebleeds and hemorrhages from the stomach or bowel. The patients in such cases show purpuric manifestations only occasionally. They have a low platelet count before operation; the quality of the blood platelets is good, though they are diminished in number, which makes them different from thrombocytopenic purpura. Such patients do well after splenectomy. Our series at the present time consists of about fifteen. All the patients are well at present, and may be considered cured. The first splenectomy was performed in 1912. We saw the patient recently, and he is apparently cured. When he came to the hospital he had a large spleen, severe anemia, ascites and purpura. A diagnosis of Banti's disease was made, and the spleen was removed for that reason. The patient did remarkably well, and his ascites cleared up after the operation. The platelet counts were not made at that time, but the last count made was

normal. There are cases in the literature, of course, that have extended over twenty-five years. Three of the patients in this benign group have had recurrent hemorrhages from the stomach.

The third group is associated with cirrhosis of the liver. Splenectomy does not cure these patients, but the blood picture is identical with that in the second group; in addition, the patients have this disease of the liver. These cases correspond to the group described by Banti, in which the patients are in the so-called third stage. I doubt whether Banti's disease is a clinical entity, but there are three main groups, and in these groups some cases vary. Examinations of the blood in all these groups are important, because one can pick out certain cases which are curable by splenectomy. Patients with a low platelet count and without evidence of impairment of the liver make good progress. When impairment is present, the prognosis cannot be made with as much certainty as in the second group. We have performed splenectomies in cases in which the patient had some impairment of the liver, because it has been said that after operation the condition in the liver subsides and the patient improves. There is a great possibility that this does occur, because, in a recent case, that of a boy, aged 12, marked cirrhosis of the liver was present. The patient has done remarkably well after splenectomy. In certain cases, splenectomy can be performed in spite of the fact that some cirrhosis of the liver is present.

M. A. GOLDZIEHER: The presentation of this interesting topic has covered the problem of portal thrombosis so thoroughly that there is little to add. Dr. Klemperer has raised the issue of Banti's disease, and has brought out some important points on this question. It is difficult to discuss Banti's disease, because all the authors who have worked with Banti's disease have different criteria for what they claim to be Banti's disease. For instance, Lubarsch, one of those cautious in diagnosing Banti's disease, says he has never seen a spleen affected by true Banti's disease. Banti himself lays the utmost stress on the fact that there is a fibro-adenia, whereas others say that fibro-adenia can be seen in spleens in which the condition cannot be described as Banti's disease. Diffuse fibrosis of the pulp is described in several cases of Banti's disease, and others do not mention it. Then again most authors have stressed the phlebosclerosis, while others do not mention it. Again, there is the question of cirrhosis of the liver in Banti's disease. Apparently the conception of Banti's disease was that of cirrhosis of the liver, anemia, preceded by the onset of splenomegaly, and a spleen out of proportion to the disease of the liver. In the case reported, it seems that cirrhosis was not present, as the drawing indicates, and Dr. Klemperer says there was none. This again brings up the question whether Banti's disease is a hepatosplenic disease, or whether it is a splenic disease pure and simple. We must be careful in the diagnosis of Banti's disease, because the term is used so indiscriminately. The diagnosis is made by many medical men if a large spleen is found, a certain amount of anemia, and more or less indication of a disturbance in the liver, with or without definite evidence of cirrhosis. This term should be used more carefully. Of great importance also is the question of thrombocythemia, and I think the evidence brought forth here that thrombocythemia is the main factor in the thrombosis of the portal vein is convincing. On the other hand, Dr. Klemperer points to the fact that there is a phlebosclerosis, and phlebosclerosis, in my experience at least, is one of the conspicuous observations in so-called Banti's disease. I am at a loss to decide whether or not this is a case of Banti's disease. I must confess I do not know what Banti's disease is, but I think that so far as the consensus of opinion goes, the outstanding features of Banti's disease were present in this case.

DAVID MARINE: I should like to ask why Dr. Klemperer used the term "cavernous transformation of the portal vein" rather than the more descriptive one of thrombosis with canalization.

PAUL KLEMPERER: The term "cavernous transformation of the portal vein" was applied only for the reason that the same type of case is described in the literature as cavernous transformation of the portal vein and the periportal tissue. It is used for canalized thrombosis of the portal vein. Five or six cases are described in the literature, and mention is made when there is an actual cavernoma within the lesser omentum; this was considered by one of the authors as an angioma, by two as malformations and by two others as angiomas on the basis of malformation. But the term "cavernous transformation" was applied in this case only in regard to reports in the literature to bring my observation in accord with them.

In regard to Dr. Goldzieher's remarks, I hope I made myself clear enough to point out that anatomically and after the full postmortem observations, the case was not a so-called Banti's disease. But the case clinically gave the strong impression of Banti's disease; so the patient was submitted to splenectomy, and I recall that there was this comment on the chart: "This is a case of Banti's disease, and in order to prevent the further fatal course of the disease, we recommend splenectomy." Furthermore, the picture of the spleen is, I think, fully in accord with the description given by Dürr for a spleen which is commonly considered as Banti's spleen. I think that Dürr's paper published in 1924 can be accepted as the last word as to what should be required as the criteria for the so-called Banti's spleen. It was apparently authorized by Banti, because it was preceded by a correspondence between Banti and Aschoff. All the criteria could be found in the case here reported with the exception of phlebosclerosis. I wanted to stress particularly that the thrombosis in my case cannot be considered as the result of the endophlebitis which occurs in Banti's disease. It is a remarkable feature of this case, which was definitely diagnosed clinically as Banti's disease, and recognized histologically as Banti's disease, that the disease of the portal vein is not primary but secondary, because one must consider the thrombocythemia as the basis of the whole condition. I want to mention a case I have seen in which a clinical picture that could have been regarded as that of Banti's disease was seen in a case of portal thrombosis due to a contiguous inflammatory lesion, that is, to a severe chronic cholecystitis. The clinical diagnosis in this case was not Banti's disease.

I am sure that Dr. Rosenthal's work is the first clinical attempt to divide cases of splenomegaly with anemia and low leukocyte counts into two groups: one in which operation can be performed and one in which it cannot be performed. The latter group is possibly the portal thrombosis group. It is difficult to recognize portal thrombosis and therefore the patients are operated on and with Dr. Rosenthal's suggestion of the blood count, it is possible to recognize the thrombocythemic group and exclude such patients from operation. We will have to find more pathologic data in order to show the actual picture of splenomegaly with anemia and low leukocyte count as described by Banti. It may be a clinical, but it is not an anatomic entity.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 8, 1927

EUGENE L. OPIE, *Presiding*

LESSIONS OF RHEUMATIC FEVER COMPARED WITH LESIONS PRODUCED BY STREPTOCOCCUS CARDIO-ARTHRITIDIS. WILLIAM P. BELK, F. J. JODZIS and E. FENDRICK.

Our purpose is to compare lesions produced in three of six rabbits and in one of two horses infected with *Streptococcus cardio-arthritis* with lesions in people. Two of the rabbits were killed by the first injection within a few

hours. One other infected with a strain of streptococcus designated as R9, did not develop any lesions. Two of the remaining three infected with strain R1, Dr. Small's original strain, which was recovered by blood culture in a case of acute rheumatic fever, developed definite lesions of the heart, and two developed lesions of the joints. The coccus was recovered in the first case of carditis, was used to infect the second, and in turn was recovered from the heart blood and vegetations of this animal. In both instances, a gram-negative bacillus of the colon type was present in the cultures.

While agreeing in all respects with the conventional conception of the significance of Aschoff bodies, we think it justifiable to take a somewhat broader view of the lesions in cases of rheumatic fever. As these bodies are found in only a proportion of the cases, it seems obvious that this lesion must represent only one stage in the development of a progressive inflammatory process. As a hypothesis which we hope to support more strongly by further study, we advance a marked stimulus to proliferation on the part of the endothelial cells in involved areas as the characteristic manifestation of rheumatic fever. This is manifest in all stages of the disease, except in the scars. The endothelium of small arterioles and capillaries seems to be most, and probably first, affected; this has been emphasized by Coombs and others. There results show some degree of starvation and damage to minute areas of tissue from this vessel occlusion. Reaction about the damaged area, and stimulation of the extravascular endothelium produce the nodules, in which, at some stage, giant cells appear.

We feel that if the experimental lesions secured in our preliminary study and demonstrated are not characteristic of rheumatic fever, they are at least similar to those of this disease, and offer support for our hypothesis.

LESIONS OF THE BRAIN IN RHEUMATIC FEVER. N. W. WINKELMAN. (From the Wards and Laboratory of the Philadelphia General Hospital.)

Four cases of acute rheumatic fever were presented. The same kind of underlying basic changes were present in all, but variations occurred according to the severity and duration of the disease. There is, apparently, a specific action of the virus or its toxin on the cells lining the smallest cerebral vessels, with secondary changes resulting from this.

The first case was that of a white boy, aged 11, in whom the rheumatic fever was complicated by pericarditis and endocarditis, with cerebral signs of choreiform movements and delirium. The brain showed an intense swelling of the intimal cells of the small vessels only, the condition having lasted but a short time before secondary changes took place. The striatum showed a moderate yet definite destruction of the small cells, with preservation of the large ganglionic elements.

The second case occurred in a white man, aged 32, with rheumatism complicated by unusual lethargy, which was thought to be the result of encephalitis. He developed purpuric spots on the body. Dr. Small believed that it was the encephalitic form of rheumatic fever with delirium, restlessness, twitching, muscle rigidity and suspicious Kernig sign. Gross examination of the brain showed purpuric spots throughout the white matter. Microscopically, these proved to be areas of necroses surrounded by collections of glial cells.

The third case was that of a woman, aged 33, with a history of rheumatic fever and following this a mental condition which was thought to be melancholia. Mentally, she was confused, retarded, refused to speak, dejected, catatonic and had to be fed with a spoon. She never talked; she was suicidal and had visual hallucinations. Autopsy revealed rheumatic endocarditis and myocarditis, while the brain showed serous meningitis with proliferative endarteritis in the smallest cerebral vessels with resulting small areas of softening in the cortex.

Case 4 was that of a white girl, aged 9, with a history of mild attacks of rheumatism with involvement of the joints. Headache, fever and mild delirium began, and twelve days before death hemiplegia of the left side developed. On admission to the hospital, a flaccid hemiplegia was noted with pathologic reflexes and cardiac murmurs and friction rub. Autopsy, which was performed two hours after death, revealed acute vegetative endocarditis and multiple infarcts of the lungs, spleen and kidneys. The brain showed two kinds of lesions: (1) lesions due to infarction and (2) peculiar nodules which in structure and cell make-up corresponded in all details to the nodules described by Aschoff in the heart in patients with acute rheumatic fever. Differential staining (Unna-Pappenheim) gave the characteristic picture in these cells, of blue nuclei with intensely red cytoplasm, morphologically distinct from plasma cells which give a similar coloration with this stain.

RHEUMATIC PNEUMONITIS. JOHN EIMAN and BENJAMIN A. GOULEY.

Rheumatic pneumonia or pneumonitis has been noted with some frequency in cases in which severe infections of rheumatic fever are present, but it has not, to our knowledge, been described as a specific pathologic entity. It differs from the ordinary bronchopneumonia and lobar pneumonia in both the clinical and pathologic pictures.

Two cases were studied at necropsy at the Philadelphia General Hospital and one at the Presbyterian Hospital.

The first one was typical of the acute pulmonary lesion of rheumatic fever. There was, of course, the usual acute pericarditis and mediastinitis. The trachea and larger bronchial branches did not show any inflammatory change.

Both lungs were enlarged, fairly bulky and did not collapse. The lower lobes were firm and solid, sections from them sinking in water. They did not crepitate, but their cut surface was unusually smooth as compared to the granular surface of ordinary pulmonary consolidation. The surface was fairly dry and somewhat edematous and oozy in the less involved areas. The lesion resembled atelectasis in its liver-like consistency, but gross evidence of collapse was not evident, as the lungs remained bulky. The overlying pleura was mildly dull.

Histologically, there was an acute interstitial infiltration, nonsuppurative and perivascular in distribution. This interstitial change was prominent in some areas, the new cells heaping up into seminodular or nodular lesions. The infiltration consisted of large, deeply stained cells, with vesicular nuclei, often multinucleated and showing a marked basophilic staining reaction. They also took the Unna-Pappenheimer stain, the cytoplasm staining red. In many collections there were large numbers of these cells; sometimes they comprised the larger part of the exudate in the most acute phase. With them, one noted a varying number of plasma cells, lymphocytes and an occasional polymorphonuclear leukocyte. Fibrin and detritus helped to complete the picture.

Some of the alveoli were filled with serum, usually little fibrin, and others with blood where the inflammatory process was most acute. In general, the cellular content of this alveolar exudate was scanty. The lining epithelium was desquamated, and where there had been a hemorrhage, a small number of polymorphonuclears was found.

All blood vessels were congested. The smaller vessels showed a marked endothelial hyperplasia, apparently the source of the large mononuclear exudate. One occasionally noted infiltrations of these cells into the walls of the larger blood vessels, into the adventitia and media. Thrombi were not noted.

In summary, the histologic study of these lungs showed an acute interstitial inflammatory process, apparently hematogenous in origin, with hyperemia, edema and a characteristic cellular exudate, perivascular, consisting of large endothelial cells, giant cells, plasmocytes, lymphocytes and a few polymorpho-

nuclears, the distribution of this exudate and its general appearance being identical with the cardiac lesions in rheumatic fever and occurring in such a case.

OBSERVATIONS BEARING ON THE RELATIONSHIP OF *STREPTOCOCCUS CARDIO-ARTHRITIDIS* TO RHEUMATIC FEVER. JAMES C. SMALL.

Based on a study of more than 100 strains, *Streptococcus cardio-arthritis* has been found to represent a distinct immunologic species. It does not produce hemolysis or greenish discoloration about the colony when it is grown on blood agar. The observations associating *Streptococcus cardio-arthritis* with rheumatic fever have been based on a study of more than 180 patients. *Streptococcus cardio-arthritis* has been found constantly in cultures from the throat of patients with rheumatic conditions. It has been recovered in four instances in blood cultures taken from patients with acute rheumatic fever.

Experimental lesions have been produced in animals (rabbits and horses). These closely resemble the spontaneous lesions of rheumatic fever. Early in the initial attack of rheumatic fever, agglutinins for *Streptococcus cardio-arthritis* are absent or of low titer in the patient's blood serum. They increase during the course of the disease, but seem to disappear early following recovery.

The opsonins for *Streptococcus cardio-arthritis* in the patient's serum are small in amount during the acute stage of the disease. The amount increases during the unfavorable course of the disease regardless of the mode of treatment, and persist at a high level during convalescence and following recovery.

Prompt beneficial effects follow the administration of the monovalent antiserum of *Streptococcus cardio-arthritis* in patients with rheumatic fever. These effects occur with regularity and become more and more significant as the number of patients treated increases. They have been observed in acute arthritis, endocarditis, carditis, pericarditis, pleuritis, pneumonitis and the subcutaneous nodules of rheumatic fever. There is a direct quantitative relationship between the quantity of antiserum administered and the effects obtained. These effects differ from the nonspecific foreign protein reaction. The antiserum has been concentrated by precipitation of the globulin fraction, and the volume of effective dose has been reduced accordingly. An amount of from 20 to 40 cc. represents the effective dosage.

Striking beneficial responses appear in chorea. These are manifested by disappearance of the choreic movements, by clearing up of speech defects and by the return of muscle coordination within from one to seven days, depending on the severity of the case. Early in the work when antiserum alone was used in treatment, occasional relapses appeared in patients suffering from grave, deep-seated rheumatic involvements. In each instance these occurred at the end of from four to five weeks following administration of the antiserum. These relapses were eliminated by beginning the use of a vaccine of *Streptococcus cardio-arthritis* during this interval. Focal and general reactions follow the injections of vaccine of *Streptococcus cardio-arthritis* in patients with rheumatic conditions. These are manifested by exacerbations of the joint symptoms, by febrile reactions, anorexia, loss of weight, abdominal cramps or vomiting, precordial pain, cardiac irregularities, muscular twitchings, emotional instability, wakefulness, increase in leukocytes and by depression of the opsonic index.

Skin tests have been practiced, and data concerning them have tended to demonstrate the complex character of the processes involved in these local reactions. In some instances, the reaction appears to be excited by the direct irritating effect of a toxic antigen, while in others, the local reactions appear to be of the nature of the Arthus phenomenon.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Dec. 12, 1927

DALLAS B. PHEMISTER, President, in the Chair

CHRONIC LOCALIZED STREPTOCOCCUS INFECTIONS IN DOGS (EXPERIMENTAL FOCAL INFECTION). G. BERNICE RHODES and CARL W. APFELBACH. (From the Pathological Laboratories of the Presbyterian Hospital and the Norman Bridge Pathological Laboratory of Rush Medical College of the University of Chicago.)

A method for producing chronic abscesses in the spleen and sacrospinalis muscles of dogs, also applicable to other parts of the body, was described. The principle underlying the method was derived from the well known fact that foreign bodies and sequestrums frequently produce chronic infections in man. A piece of sterile cancellous bone was immersed in ascitic infusion broth, and the latter was inoculated with the bacterium of choice. After from twenty-four to forty-eight hours, the bone was implanted in the body of a dog. When the spleen is used, the arteries to the pole of the spleen in which the bone is implanted are ligated.

A dog's spleen with two abscesses, each about 2.5 cm. in diameter and of one and two months' duration, respectively, was demonstrated. *Streptococcus hemolyticus* had been implanted originally and was isolated from both abscesses at the death of the dog. Cultures of the blood during life were sterile, although the number of leukocytes fluctuated, indicating absorption.

DISCUSSION

E. R. LONG: I am interested in this method because of the possibility of causing localized infections in animals with *Bacillus tuberculosis*. Perhaps focal lesions such as those of the suprarenal glands in patients with Addison's disease, and not a generalized infection, can be produced experimentally by this method.

DALLAS B. PHEMISTER: Bullets healed into tissues remain quiescent, but with dead bone there is always a sinus. This difference is regarded due to channels in bone harboring bacteria which are inaccessible to the soft tissues and are not destroyed.

LYMPHANGIO-HEMANGIOMA OF THE LIVER OF A DOG. S. F. ARQUIN.

The tumor was found accidentally in an old dog, and is reported because of its infrequency. There seems to be no other report like it. A portion of the liver extended through an opening in the diaphragm into the left thoracic cavity. The abdominal portion, which was hyperemic, was otherwise unchanged, but the thoracic portion was covered by dilated pink lymph vessels from 0.25 to 2 mm. in diameter. These lymphatics extended downward, forming a thick mass in the hepatoduodenal septum. The gallbladder was in the thorax, and the surface also had many dilated vessels. The lymph glands along the portal vein were large, and were changed in a similar way.

Microscopic preparations of both portions of the liver contained many dilated thin-walled vessels, lined by endothelium, filled with a pink staining, homogenous material, and extended inward from the surface along the portobiliary septums. Around these vessels was a cellular mesenchymatous tissue, with round or oval, darkly staining nuclei, and a small amount of cytoplasm. This tissue contained newly formed lymph vessels and seemed to invade the substance of the liver. The blood vessels of the liver were markedly distended, and increased in number.

DISCUSSION

E. F. HIRSCH: Many years ago Dr. Bassoe reported to this society a case of true endothelioma of the chest. It was composed of many capillaries which formed a continuous chain from the axillary to the groin lymph glands, but it had not produced metastases elsewhere.

H. JAFFÉ: I know of a similar condition of the arm in which there were many lymph channels.

MESENCHYMATOUS TUMORS OF THE LUNG. I. PILOT.

Two chondromas, a fibroma, a fibromyoma and a fibrosarcoma occurring in separate patients were reported.

The complete account will be published in the ARCHIVES OF PATHOLOGY.

DISCUSSION

DALLAS B. PHEMISTER: The thickenings along the shaft of the bones have been designated as pulmonary osteo-arthritis, or periosteal proliferation and occur with primary or secondary tumors of the lungs, bronchiectases and abscesses of the lungs. Some mechanical interference with respiration was thought to be the cause of these changes. Dr. Potter, however, injected paraffin into the thorax of dogs in quantities sufficient to cause a marked interference with respiration, and in these animals changes of the bones did not occur.

H. JAFFÉ: I wonder whether tumors of the lung in mice are associated with such changes of the bones.

THE LOCATION OF METASTATIC TUMORS IN THE BRAIN. GILBERT J. RICH.

The results of a study of a brain containing twenty-three separate tumors were reported. The tumors were secondary to a small round cell growth in the mediastinum regarded as a sarcoma. The tumors were measured, described and charted in an effort to determine the factors responsible for their location. Conclusions from this study and from rather meager references to the subject in available literature were that the distribution and structure of the blood vessels favor location of metastatic tumors in the cortex and subcortical white matter.

Book Reviews

SEGREGATION AND AUTOGAMY IN BACTERIA. A CONTRIBUTION TO CELLULAR BIOLOGY. By F. H. STEWART, M.A., D.Sc., M.D., Major, Indian Medical Service (Ret.). Pp. 104, 4 plates. Price, 7 shillings, 6 pence, net. London: Adlard & Son, Limited, 1927.

The segregation and autogamy hypothesis is found to be consistent with the facts of bacterial variation presented; with the cytology of sporing bacteria as known; with the observations by Preisz that papillae arise from spores in spore-bearing races; with the mode of growth of bacterial plate colonies, the cessation of their growth when papillae form and other facts in regard to papillation and variation. "The mutation or adaptation hypothesis" or any other hypothesis is not consistent with these facts.

The author then traces the life history of a bacterium as follows: "If it is placed in new surroundings with sufficient food it multiplies quickly by simple fission (colony formation). This vegetative phase is stopped by an intrinsic force, but it can be either lengthened or shortened by external conditions (amount of food available, moisture, crowding), and it can be continued indefinitely by frequent change of surroundings. Shortly before vegetative growth stops the second phase of the life cycle begins, in which a few out of the great number of bacteria in a colony (either on solid or in liquid nidus) go through segregation, autogamic conjugation, and, under certain circumstances, variation. In spore-bearing races the zygote forms the spore. Segregation in bacteria is the same as in the higher forms; in it allelomorphous couples of the organism divide. We know little about the mechanism of autogamy, but it seems not unlikely that before segregation takes place each allelomorphous couple is represented in the 'anterior' and 'posterior' halves of the bacterium (Schaudinn and Dobell's presporing division), and that, after segregation, and if nothing disturbs them, the 'right hand' allelomorphs of one half of the body unite with the 'left hand' allelomorphs of the other. At least this is as good a mental picture as any other. But, if a definite external stimulus is at the moment bearing on a heterozygous bacterium, then in the one pair (anterior and posterior) of allelomorphous couples which is concerned with the stimulus, the dominant allelomorphs are dissipated (as primitive polar bodies?) the recessives come together, and the bacterium varies. The recessive so formed may also vary in simple fission if one of its recessive allelomorphs is not pure but is loaded with a fragment of the dominant factor. It may then vary in two directions—by increasing, or decreasing, this fragment."

PRACTICAL BACTERIOLOGY, BLOOD WORK AND ANIMAL PARASITOLOGY. By E. R. STITT, M.D., LL.D., Rear Admiral, Medical Corps and Surgeon General, U. S. Navy. Eighth edition, revised and enlarged. Price, \$6. Pp. 837. Philadelphia: P. Blakiston's Son & Company, 1927.

Dr. Stitt's book has not undergone such radical changes but that one familiar with the seventh edition would still feel at home in most of the chapters of the new eighth and enlarged edition. That great efforts have been made to bring the eighth edition up to date is, however, evident throughout the new volume. The front fly-leaf ushers in changes with a terse description of the new Neubauer blood counting chamber and its manipulation. Three improved illustrations of this chamber ruling also amplify the text in chapter XIII. The revision in the chapters on blood is thorough, and a section dealing with the blood diseases, thrombocytopenia, Schönlein's disease, Henoch's purpura, hemophilia and hemorrhagic disease of the new-born imparts a wealth of sound information in a small space. Revisions in bacterio-

logic and zoologic nomenclature conform to the latest standards, and for those who cannot keep up with these irksome philologic changes the old nomenclature is also inserted. A new section on tests on the function of the liver gives evidence of a careful selection of those most likely to be of a permanently valuable nature. Chapter XXVIII, which deals with the diagnosis of infections of the teeth, is an innovation dealing with this subject as fully as the many conflicting views on its various phases and limited space permit. The outstanding addition is the elaborate presentation of the Kahn test with five illustrations in this section. Paragraph headings are: "Reagents Employed, Routine Test with Serum, Outline of Kahn Test and Interpretation of Results, Quantitative Procedure, Presumptive Procedure, Spinal Fluid Procedure," etc. Sixty-seven new pages swell the text total to 811, and the use of small type whenever possible has still further increased the space available for desirable alterations and additions.

KOLLOIDCHEMIE DER WASSERBINDUNG. Eine kritische und experimentelle Untersuchung der Wasserbindung in Kolloiden und ihrer Beziehungen zu den Problemen der Wasserbindung in Physiologie, Medizin und Technik. Von Martin H. Fischer, Doktor der Medizin und Pharmazie, Eichberg-Professor der Physiologie an der Universität Cincinnati. Zweite erweiterte, von Verfasser durchgesehene deutsche Ausgabe. Neue Uebersetzung der dritten amerikanischen Auflage von Dr. Katharina Popp. Band I Wasserbindung in Odemen, Mit 142 Abbildungen. Pp. 368. Dresden und Leipzig: Verlag von Theodor Steinkopff, 1927.

This pretentious volume of nearly 400 pages is saved from prolixity by the number and variety of experimental protocols offered to support the author's theme. Whether one agrees or not with the conclusions drawn, one must admire the persistence with which Fischer has elaborated his views on the interchange and holding of water in the tissues in various physiologic and pathologic activities. The volume is initiated by observations on simple phenomena of colloidal chemistry, with evident care in the selection of materials that exhibit reactive properties similar to those of the animal tissues later considered. On the basis of altered fluid capacity dependent on variations in acid content, theories of many activities of the tissues are developed. Excess of fluids in the tissues, or edema, is said to be associated constantly with abnormal formation or accumulation of acids in the tissues or with circumstances which tend toward such disposition. Likewise, absorption and secretion, the holding of fluid by the blood and lymph colloids and by muscle tissue as well as the crenation and lysis of red blood cells are all explained on similar grounds. The clarity of the style and the forcefulness of the exposition are faithfully reproduced in this German translation.

Books Received

HISTORICAL SURVEY OF RESEARCHES ON THE STREPTOCOCCI (with Special Reference to the Importance of Differential Media and Microphotography as an Aid to Their Classification and Identification). By David and Robert Thomson. Vol. 3. Pp. 316. Annals of the Pickett-Thomson Research Laboratory, 1927.

MOSQUITO SURVEYS. A Handbook for Anti-Malarial and Anti-Mosquito Field Workers. By Malcolm E. McGregor, Entomologist, Wellcome Field Laboratory, Wisley, Surrey, England. Price, \$5.50. Pp. 282. Three maps and 9 other illustrations. New York: William Wood & Co., 1928.

ALASTRIM ET VARIOLE. Vaccine. Encéphalites Postvaccinales. By Ricardo Jorge. Pp. 181. Lisbonne. Institut Central D'Hygiène, 1927.

I VACCINI ANTIRABICI FENICATI E LORO ODIERNE APPLICAZIONI. Del Dott. By Vittorio Puntoni, Professore di Batteriologia Nella R. Università E Vice Direttore Dell 'Istituto Antirabico di Roma. Pp. 116. Rome: S. Bucciarelli, 1927.

CLINICAL PATHOLOGY. By P. N. Panton, Clinical Pathologist to the London Hospital and Director of the Clinical Laboratories, and J. R. Marrack, Chemical Pathologist to the London Hospital. Ed. 2. Price, 15 shillings. Pp. 459, with 12 plates (10 colored) and 51 illustrations in the text. London: J. & A. Churchill, 1927.

A METHOD FOR ESTIMATING THE POTENCY OF SMALLPOX VACCINE. The Immunological Relationship of Alastrim and Mild Smallpox. Hygienic Laboratory Bulletin no. 149. Washington, D. C.: United States Public Health Service, 1927.
